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CONDENSED BENZENE DERIVATIVE, ITS MANUFACUTRING METHOD, AND AGENTS

[Shukugo Benzen Yudotai, Sono Seizoho Oyobi Zai]

Tetsuya Aono et al.

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Inventor	:	Tetsuya Aono
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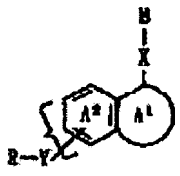
Specification

1. Title of the invention

Condensed Benzene Derivative, Its Manufacturing Method, and Agents

2. Claims /2

1. A condensed benzene derivative or its salt, characterized by being represented by a general formula. (Structure 1)



(In the formula, A^1 ring represents a 5 or 6-membered ring-shaped hydrocarbon that may also be further substituted; A^2 ring represents a benzene ring that may also be further substituted; B represents a heterocyclic group that may also be substituted; R represents a ring-shaped hydrocarbon group that may also be substituted or a heterocyclic group that may also be

[1] Numbers in the margin indicate pagination in the foreign text.

substituted; and X and Y respectively represent a coupler or divalent group.)

2. The compound of Claim 1, characterized by the fact that B is a 5 or 6-memberred heterocyclic group containing a nitrogen that may also be substituted.

3. The compound of Claim 1, characterized by the fact that B is an imidazolyl group that may also be substituted.

4. The compound of Claim 1, characterized by the fact that R is a ring-shaped hydrocarbon group that may also be substituted.

5. The compound of Claim 1, characterized by the fact that R is a phenyl that may also be substituted.

6. The compound of Claim 1, characterized by the fact that the divalent group respectively represented by X and Y is a divalent lower aliphatic group that may also be substituted by an oxo group, -NR'-(R' represents a hydrogen atom or lower alkyl group), -O-, -S-, -COO-, -COS-, -CONR'- (R' has the same meaning as the above-mentioned one), -SO-, $-SO_2-$, -N=N-, or lower alkylene via one or two atoms selected from oxygen, nitrogen, and sulfur atoms.

7. The compound of Claim 1, characterized by the fact that X is a coupler.

8. A medical composition, characterized by including the compound of Claim 1.

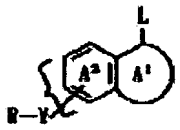
9. A steroid C_{17-20} lyase inhibitor, characterized by including the compound of Claim 1.

10. An antitumor agent, characterized by including the compound of Claim 1.

11. The antitumor agent of Claim 10, characterized by being a preventing and treating agent of a breast cancer or prostatic cancer, including the compound of Claim 1.

12. A method for manufacturing the compound of Claim 1, characterized by the fact that a compound represented by a general formula

(Structure 2)



(in the formula, L represents a leaving group; and the other symbols have the same meanings as the above-mentioned ones) or its salt and a compound represented by a general formula

HX-B

(in the formula, X and B have the same meanings as those described in Claim 1) or its salt are reacted.

3. Detailed explanation of the invention

[0001]

(Technical field of the invention)

The present invention pertains to a medicine, especially a useful new condensed benzene derivative as a steroid C_{17-20} lyase inhibitor, its manufacturing method, and medical compositions being constituted by including it.

[0002]

(Prior art)

Steroid C_{17-20} lyase generates an androgen, using 17-hydroxypregnenolone and 17-hydroxyprogesterone being generated from a cholesterol as a matrix. Therefore, the steroid C_{17-20} lyase inhibitor suppresses the generation of androgen or estrogen being synthesized from the androgen and can be used as a preventing and treating drug of diseases in which the androgen or estrogen is a malignant factor. As the diseases in which the androgen or estrogen is a malignant factor, prostatic cancer, prostatic hypertrophy, masculinization, hypertrichosis, breast cancer, uterine cancer, mastitis, hysteromyoma, endometriosis, etc., are mentioned. Up to now, steroid type compounds and non-

steroid type compounds have been known. The steroid type compounds, for example, are presented in WO 92/15404, WO 93/20097, EP-A 288053, EP-A 413270, etc. As the non-steroid type compounds, for example, (1H-imidazole-1-yl) methyl-substituted benzimidaozle derivative is presented in Japanese Kokai Patent Application No. Sho 64[1989]-85975, carbazole derivative is presented in WO 94/27989 and WO 96/14090, azole derivative is presented in WO 95/09157, and 1H-benzimidazole derivative is presented in US 5,491,161.

[0003]

(Problems to be solved by the invention)

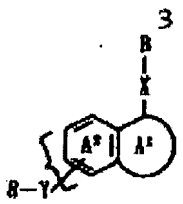
At present, the steroid C_{17-20} lyase inhibitor usable in the medical field cannot be obtained yet, and the early development of a steroid C_{17-20} lyase inhibitor having high usefulness as a medicine is expected.

[0004]

(Means to solve the problems)

These inventors repeatedly earnest researches to find out an excellent androgen synthesized inhibitor, especially a steroid C_{17-20} lyase inhibitor. As a result, it was discovered that a condensed benzene derivative or its salt represented by a general formula

(Structure 3)

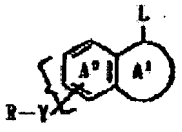


/3

(in the formula, A^1 ring represents a 5 or 6-membered ring-shaped hydrocarbon that may also be further substituted; A^2 ring represents a benzene ring that may also be further substituted; B represents a heterocyclic group that may also be substituted; R represents a ring-shaped hydrocarbon group that may also be substituted or a heterocyclic group that may also be substituted; and X and Y respectively represent a coupler or divalent group.) with a specific chemical structure having a substituent R-Y- and a specific position substituent B-X- of an A^1 ring part at a specific position of a benzene ring part of a condensed benzene skeleton was synthesized for the first time and unexpectedly, the compound obtained had excellent properties as a clinical medicine with little toxicity as well a steroid C_{17-20} lyase inhibitor with especially excellent medical usages based on it specific chemical structure. The present invention was completed based on the knowledge.

[0005] In other words, the present invention pertains to (1) a condensed benzene derivative or its salt, characterized by being represented by a general formula.

(Structure 4)



(In the formula, A^1 ring represents a 5 or 6-membered ring-shaped hydrocarbon that may also be further substituted; A^2 ring represents a benzene ring that may also be further substituted; B represents a heterocyclic group that may also be substituted; R represents a ring-shaped hydrocarbon group that may also be substituted or a heterocyclic group that may also be substituted; and X and Y respectively represent a coupler or divalent group.); (2) the compound described in the above-mentioned (1) in which B is a 5 or 6-memberred heterocyclic group containing a nitrogen that may also be substituted; (3) the compound described in the above-mentioned (1) in which B is an imidazolyl group that may also be substituted; (4) the compound described in the above-mentioned (1) in which R is a ring-shaped hydrocarbon group that may also be substituted; (5)

the compound described in the above-mentioned (1) in which R is a phenyl that may also be substituted; (6) the compound described in the above-mentioned (1) in which the divalent group respectively represented by X and Y is a divalent lower aliphatic group that may also be substituted by an oxo group, -NR'-(R' represents a hydrogen atom or lower alkyl group), -O-, -S-, -COO-, -COS-, -CONR'- (R' has the same meaning as the above-mentioned one), -SO-, $-SO_2-$, -N=N-, or lower alkylene via one or two atoms selected from oxygen, nitrogen, and sulfur atoms; (7) the compound described in the above-mentioned (1) in which X is a coupler; (8) a medical composition containing the compound described in the above-mentioned (1); (9) a steroid C_{17-20} lyase inhibitor containing the compound described in the above-mentioned (1); (10) an antitumor agent containing the compound described in the above-mentioned (1); (11) the antitumor agent described in the above-mentioned (10) that is a preventing and treating agent of a breast cancer or prostatic cancer, including the compound described in the above-mentioned (1); and (12) a method for manufacturing the compound described in the above-mentioned (1) characterized by the fact that a compound represented by a general formula

(Structure 5)

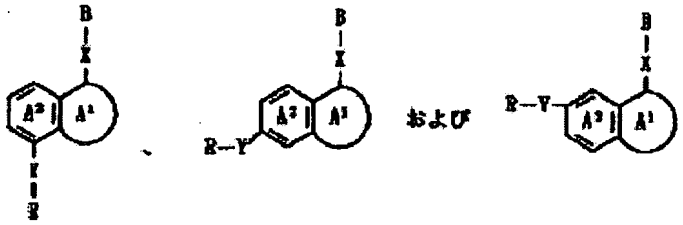
(in the formula, L represents a leaving group; and the other symbols have the same meanings as the above-mentioned ones) or its salt and a compound represented by a general formula

HX-B

(in the formula, X and B have the same meanings as those described in Claim 1) or its salt are reacted.

[0006] In the above-mentioned general formula (I), the following chemical structural formula may be included and the substitution position of R-Y- in the general formula (I) may any of three positions of the benzene ring A^2.

(Structure 6)



(In the formula, the symbols have the same meanings as the above-mentioned ones.) In the above-mentioned general formula,

(Structure 7)

represents a bicyclic condensed benzene ring that may also be substituted, A^1 ring represents a 5 or 6-membered ring-shaped hydrocarbon that may also be further substituted, and A^2 ring represents a benzene ring that may also be further substituted. As said condensed benzene ring, indane, indene, tetralin, 1,2-dihydronaphthalin, 3,4-dihydronaphthalin, and naphthalinn are mentioned, and among them, indane, indene, etc., are preferable.

[0007] As the heterocyclic group of "the heterocyclic group that may also be substituted" represented in each of B and R in the above-mentioned general formula, aromatic heterocyclic group, saturated, or unsaturated nonaromatic heterocyclic group (aliphatic heterocyclic group) having at least one /4 hetero atom of oxygen, sulfur, and nitrogen are mentioned as atoms (ring atoms) constituting a ring, and an aromatic heterocyclic group is preferable. As said aromatic heterocyclic group, for example, 5 to 7-memmbered aromatic heterocyclic group containing one sulfur atom, nitrogen, or oxygen atom, 5 to 6-membered aromatic heterocyclic group containing 2-4 nitrogen atoms, 5 to 6-membererd aromatic heterocyclic group containing

1-2 nitrogen atoms and one sulfur atom or oxygen atom, etc., are mentioned, and these aromatic heterocyclic groups may also be condensed with a 6-membered ring containing two or less nitrogen atoms, benzene ring, or 5-membered ring containing one sulfur atom. As said aromatic heterocyclic groups, for example, aromatic monocyclic heterocyclic group (for example, furyl, chienyl, pyrolyl, oxazolyl, isoxazoyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidyl, pyradinyl, triazynyl(1,3,5-triazinyl, 1,2,4-triazynyl), etc.), aromatic condensed heterocyclic group (example: benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisooxazolyl, benzothiazolyl, 1,2-benzoisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolynyl, quinazolinyl, quinoxalynyl, phthaladinyl, naphthylidinyl, purinyl, puteridinyl, carbazolyl, α-carbolynyl, β-carbolynyl, γ-carbolynyl, acrydinyl, phenoxadinyl, phenothiadinyl, phenadinyl, phenoxadinyl, phenothiazinyl, thianthrenyl, phenantridinyl, phenanthrolinyl, indolidinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-

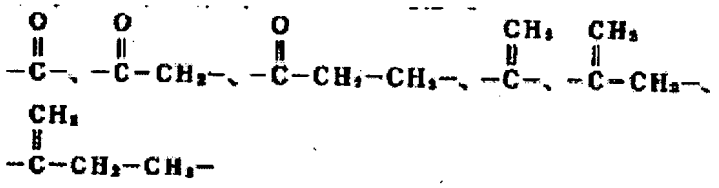
a]pyridyl, 1,2,4-triazolo[4,3-b]pyridazinyl, etc.), etc., are mentioned.

[0008] As said nonaromatic heterocyclic group, 5 to 7-membered nonraomatic heterocyclic group containing one sulfur atom, nitrogen atom, or oxygen atom or 3 to 7-membered nonaromatic heterocyclic group containing three or less heteroatoms (for example, nitrogen, oxygen, and sulfur atoms), for example, oxylanyl, azethidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetetrahydrofuryl, tiholanyl, piperidiyl, tetrahydropyranyl, morpholynyl, thiomorpholonyl, piperadinyl, homopiperidinyl, pyrrolinyl, imidazolidinyl, etc., are mentioned. Said nonaromatic heterocyclic group may also be condensed with benzene ring, 6-membered ring containing 2 or less nitrogen atoms, or 5-membered ring containing one sulfur atom, etc., and as said condensed nonaromatic heterocyclic group, for example, chromanyl, isochromanyl, indolinyl, isoindolinyl, thiochromanyl, isothiochromanyl, etc., are mentioned. As the substituent in the "heterocyclic group that may also be substituted" respectively represented by B and R, 1-3 substituents may be substituted at positions where the heterocyclic group can be substituted. As said substituent, alkoxy group (example: C_{1-4} alkoxy such as methoxy, ethoxy, and propoxy) that m ay also be substituted by 1-3 halogen atoms (for example, fluorine,

chlorine, bromine, and iodine), alkyl group (for example, C_{1-4} alkyl such as methyl, ethyl, and propoyl) that may also be substituted by 1-3 halogen atoms (for example, fluorine, chlorine, bromine, and iodine), aryl group (may also be substituted by C_{1-3} alkyl group such as methyl, ethyl, propyl, and isopropyl, C_{1-3} alkoxy group such as methoxy, ethoxy, propoxy, and isopropoxy, halogen atom such as chlorine atom and fluorine atom, hydroxyl group, amino group, nitro group, or cyano group) (for example, C6-10 aryl such as phenyl, 1-naphthyl, and 2-naphthyl), nitro group, etc., are mentioned. As preferable examples of the heterocyclic group that may also be substituted by B, for example, 5 or 6-membered heterocyclic group containing nitrogen such as imidazolyl, pyrolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, thiazolyl, isothiazolyl, oxazolyl, isooxazolyl, pyridyl, pyridazynyl, pyrimidinyl, pyrazynyl, 1,3,5-triazynyl, and 1,2,4-triazynyl are mentioned. In particular, imidazolyl, 1,2,4-triazolyl, pyridyl, etc., are preferable, and imidazolyl is most preferable. These heterocyclic groups may also be further substituted by alkoxy group (for example, C1-4 alkoxy such as methoxy, ethoxy, and propoxy) that may also be substituted by 1-3 halogen atoms (for example, fluorine, chlorine, bromine, and iodine), halogen atom (for example, fluorine, chlorine, bromine,

and iodine), or alkyl group (for example, C1-4 alkyl such as methyl, ethyl, and propyl) that may also be substituted by 1-3 halogen atoms (for example, fluorine, chlorine, bromine, and iodine). The number of substituent is 1-3 pieces.

[0009] As the "divalent group" represented by X or Y, for example, divalent lower aliphatic group that may also be substituted by an oxo group, -NR'-(R' has the same meaning as the above-mentioned one), -O-, -S-, -COO-, -COS-, -CONR'- (R' has the same meaning as the above-mentioned one), -SO-, $-SO_2-$, -N=N-, or lower alkylene via one or two atoms selected from oxygen, nitrogen, and sulfur atoms are mentioned. R' represents hydrogen atom or lower alkyl group, for example, C_{1-4} alkyl group such as methyl, ethyl, propyl, and isopropyl. As said /5 "divalent lower aliphatic group that may also be substituted by an oxo group," for example, C_{1-6} alkylene, C_{2-6} alkenylene, or C_{2-6} alkinylene that may also be substituted by one oxy group such as $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$, $-CH(CH_3)CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, -CH=CH-, -C≡C-,



(Structure 8)

are mentioned. As said "lower alkylene via one or two atoms being selected from oxygen, nitrogen, and sulfur atoms," for example, C1-4 alkylene groups via 1-2 atoms being selected from oxygen, nitrogen, and sulfur atoms such as $-CH_2O-$, $-OCH(CH_3)-$, $-CH_2CH_2O-$, $-OCH_2O-$, $-OCH_2CH_2O-$, $-CH_2NH-$, $-CH_2CH_2-$, $-NHCH(CH_3)-$, $-N(CH_3)CH_2-$, $-NHCH_2CH_2NH-$, $-CH_2S-$, $-SCH(CH_3)-$, $-OCH_2CH_2NH-$, $-OCH_2CH_2S-$, and $-SCH_2CH_2NH-$ are mentioned. As the ring-shaped hydrocarbon group in the "ring-shaped hydrocarbon group that may also be substituted" represented by R, saturated or unsaturated alicyclic hydrocarbon group, aromatic hydrocarbon group, etc., are mentioned.

[0010] As said saturated alicyclic hydrocarbon group, saturated alicyclic hydrocarbon groups having 3-12 carbons (for example, monocyclic or dicyclic C3-12 cycloalkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclobutyl, cyclooctyl, bicyclo[2,2,1]heptyl, bicycle[2,2,2]octyl, bicycle[3,2,1]octyl, bicycle[3,2,2]nonyl, bicycle[3,3,1]nonyl, bicycle[4,2,1]nonyl, and bicyclo[4,3,1]decyl) are mentioned, and saturated alicyclic hydrocarbon groups having 5-6 carbons, etc., are preferably mentioned. As said unsaturated alicyclic hydrocarbon groups, unsaturated alicyclic hydrocarbon groups

having 3-12 carbons (for example, C_{3-12} cycloalkehyl group such as 1-cyclopropenyl, 2-cyclopropenyl, 1-cyclobutenyl, 2-cyclobutenyl, 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2-cyclopentene-1-yl, 3-cyclopentene-1-yl, 2-cyclohexene-1-yl, and 3-cyclohexene-1-yl, C_{3-12} cycloalkadienyl group such as 2,4-cyclopentadiene-1-yl, 2,4-cyclohexadiene-1-yl, 2,5-cyclohexadiene-1-yl, and 2,4-cylcoheptadienyl, etc.) are mentioned. As said aromatic hydrocarbon group, monocyclic or condensed polycyclic aromatic hydrocarbon groups having 6-14 carbons, etc., are mentioned. As said aromatic hydrocarbon ring group, for example, aromatic hydrocarbon ring groups having 6-14 carbons such as phenyl, 1- or 2-naphthyl, 1-, 2-, or 9-anthryl, 1-, 2-, 3-, 4-, or 9-phenanthryl, 1-, 2-, 4-, 5-, or 6-azulenyl, and acenaphthylenyl are mentioned. Among them, C_{6-10} aryl such as phenyl, 1-naphthyl, and 2-naphthyl are preferable, and phenyl is more preferable.

[0011] The ring-shaped hydrocarbon group in the "ring-shaped hydrocarbon group that may also be substituted" represented by R may also have 1-3 optional substituents at the positions where it can be substituted. As said substituents, (1) lower alkyl group that may also be substituted, (2) lower alkoxy group that may also be substituted, (3) aryl group that may also be

substituted, (4) lower cycloakyl group or cycloalkenyl group that may also be substituted, (5) carboxyl group that may also be esterified, (6) carbamoyl group that may also be substituted, (7) amino group that may also be substituted, (8) hydroxyl group that may also be substituted, (9) thiol (mercapto) group that may also be substituted, (10) acyl group, (11) halogen (for example, fluorine, chlorine, bromine, etc.), (12) nitro, (13) cyano, etc., are mentioned. As the lower alkyl group of said lower alkyl group (1) that may also be substituted, for example, C_{1-6} alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, and isohexyl are mentioned. As the lower alkoxy group of said lower alkoxy group (2) that may also be substituted, C_{1-6} alkoxy groups such as methoxy, ethoxy, propoxy, isoopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, isopentoxy, neopentoxy, hexyloxy, and isohexyloxy are mentioned.

[0012] Said lower alkyl group (1) and lower alkoxy group (2) may also have 1-3 substituents at the positions where they can be substituted, and as said substituents, for example, halogen (for example, fluorine, chlorine, bromine, etc.), lower (C_{1-3}) alkoxy (for example, methoxy, ethoxy, propoxy, etc.), etc., are mentioned. As the aryl group of said aryl group (3) that may

also be substituted, C_{6-14} aryl groups such as phenyl, /6 naphthyl, anthryl, phenanthryl, and acenaphthylenyl are mentioned, and among them, phenyl, 1-naphthyl, 2-naphthyl group, etc., are preferable. As the cycloalkyl group of said lower cycloalkyl group (4) that may also be substituted, C_{3-7} cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl are mentioned. As the cycloalkenyl group of said lower cycloalkenyl group that may also be substituted, C_{3-6} cycloalkenyl groups such as cyclopropenyl, cyclobutenyl, cyclopentenyl, and cyclohexenyl are entioned. Said aryl group (3) and lower cycloalkyl group (4) or lower cycloalkenyl group (4) may also have 1-5 optional sustituents, preferably 1-3 substituents at the positions where they can be substituted, and as said substituents, alkoxy group (for example, C_{1-3} alkoxy such as methoxy, ethoxy, and propoxy), halogen atom (for example, fluorine, chlorine, bromine, and iodine), alkyl group (for example, C_{1-3} alkyl such as methyl, ethyl, and propyl), amino group, hydroxyl group, nitro group, cyano group, etc., are mentioned.

[0013] As said carboxyl (5) that may also be estrified, carboxyl group, (lower(C_{1-6}) alkoxy)carbonyl (for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropylcarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-

butoxycarbonyl, sec-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, neopentyloxycarbonyl, tert-pentyloxycarbonyl, hexyloxycarbonyl, etc.), (C_{6-10} aryl)oxycarbonyl (for example, phenoxycarbonyl, 1-naphthoxycarbonyl, etc.), (C_{7-10} aralkyl)oxycarbonyl (for example, benzyloxycarbonyl, etc.) (phenyl-C_{1-4} akyloxy)carbonyl, etc.), etc., are mentioned. Among them, carboxyl group, methoxycarbonyl group, ethoxycarbonyl group, etc., are preferable.

[0014] As the substituents of said carbamoyl group (6) that may also be substituted and the amino group (7) that may also be substituted, for example, C_{1-6} alkyl group that may also be substituted (for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, etc.), C_{3-6} cycloalkyl group that may also be substituted (for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), C_{6-10} aryl group that may also be substituted (for example, phenyl, 1-naphthyl, 2-naphthyl, etc.), C_{7-12} aralkyl group that may also be substituted (for example, phenyl-C_{1-4} alkyl such as benzyl and phenethyl, naphthyl-C_{1-2} alkyl, etc.), C_{6-10} arylsulfonyl group that may also be substituted (for example, benzenesulfonyl, 1-naphthalenesulfonyl, 2-naphthalenesulfonyl, etc.), etc., are

mentioned. These substituents may be the same or different, and one or two of them may also be substituted. As the substituents in C_{1-6} alkyl group that may also be substituted, C_{3-6} cycloalkyl group that may also be substituted, C_{6-10} aryl group that may also be substituted, C_{7-12} aralkyl group that may also be substituted, and C_{6-10} arylsulfonyl group that may also be substituted, halogen (for example, fluorine, chlorine, bromine, etc.), alkoxy group that may also be substituted by 1-3 halogen atoms (for example, C_{1-4} alkoxy such as methoxy, ethoxy, and propoxy), alkyl group that may also be substituted by 1-3 halogen atoms (for example, C_{1-4} alkyl such as methyl, methyl, and propyl), nitro group, etc., are mentioned, and one to five of them may also be substituted. Also, in the amino group (7) that may also be substituted, two substituents of nitrogen atoms may also form a ring-shaped amino group along with the nitrogen atoms, and as examples of the ring-shaped amino group, 1-azetidinyl, 1-pyrrolidinyl, piperidinyl, morpholino, htiomorpholino, 1-piperazinyl, etc., are mentioned.

[0015] As the substituents of said hydroxyl group (8) that may also be substituted and thiol group (9) that may also be substituted, for example, C_{1-6} alkyl group that may also be substituted (for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl tert-butyl, pentyl, isopentyl,

neopentyl, hexyl, isohexyl, etc.), C_{3-6} cycloalkyl group that may also be substituted (for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc.), C_{6-10} aryl group that may also be substituted (for example, phenyl, 1-naphthyl, 2-naphthyl, etc.), C_{7-12} aralkyl group that may also be substituted (for example, phenyl-C_{1-4} alkyl such as benzyl and phenethyl, naphthyl-C_{1-2} alkyl, etc.), etc., are mentioned. Said C_{1-6} alkyl group, C_{3-6} cycloalkyl group, C_{6-10} aryl group, and C_{7-12} aralkyl group may also have 1-5 substituents at optional positions where they can be substituted, and as said substituents, for example, halogen (for example, fluorine, chlorine, bromine, etc.), alkoxy group that may also be substituted by 1-3 halogen atoms (for example, C_{1-4} alkoxy such as methoxy, ethoxy, and propoxy), alkyl group that may also be substituted by 1-3 halogen atoms (for example, C_{1-4} alkyl such as methyl, methyl, and propyl), nitro, amino, cyano, etc., are mentioned.

[0016] As said acyl group (10), for example, formyl, carbonyl group substituted by a hydrocarbon group that may also be substituted, sulfinyl group substituted by a hydrocarbon group that may also be substituted, sulfonyl group substituted by a hydrocarbon group that may also be substituted, etc., are /7 mentioned. As said "hydrocarbon group that may also be substituted," for example, C_{1-6} alkyl group that may also be

substituted, C_{6-10} aryl group that may also be substituted (for example, phenyl, naphthyl, etc.), C_{7-12} aralkyl group that may also be substituted (for example, phenyl-C_{1-4} alkyl, naphthyl-C_{1-2} alkyl, etc.), etc., are mentioned. In other words, as said acyl group, formyl group, (C_{1-6} alkyl)carbonyl group, (C_{3-6} cycloalkyl)carbonyl group, (C_{6-10} aryl)carbonyl group, (C_{7-12} aralkyl)carbonyl group, (C_{1-6} alkyl)sulfonyl group, (C_{3-6} cycloalkyl)sulfonyl group, (C_{6-10} aryl)sulfinyl group, (C_{7-12} aralkyl)sulfinyl group, (C_{1-6} alkyl)sulfonyl group, (C_{6-10} aryl)sulfonyl group, (C_{7-12} aralkyl)sulfonyl group, etc., are mentioned. These acryl groups may also have 1-5 substituents at optional positions where they can be substituted, and as said substituents, for example, halogen atom (for example, fluorine, chlorine, bromine, and iodine), lower alkoxy group (for example, C_{1-4} alkoxy such as methoxy, ethoxy, and propoxy), and lower alkyl group (for example, C_{1-4} alkyl such as methyl, methyl, and propyl) are mentioned.

[0017] If R is an aromatic hydrocarbon group that may also be substituted, as preferable examples of the substituents having said aromatic hydrocarbon group, C_{1-3} alkyl group such as methyl, ethyl, propyl, and isopropy, C_{1-3} alkoxy group such as methoxy, ethoxy, propoxy, and iopropoxy, halogen atom such as chlorine atom and fluorine atom, hydroxyl group, amino group, nitro

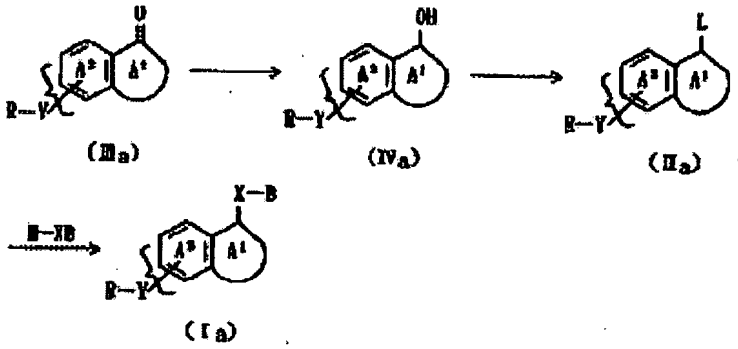
group, cyano group, etc., are mentioned. The number of these substituents is 1-5 pieces. Said C_{1-3} alkyl group and C_{1-3} alkoxy group may also have 1-3 halogens (for example, fluorine, chlorine, and bromine) at the positions where they can be substituted. A^2 ring and A^1 ring may have 1-3 optional substituents at the positions where they can be substituted, and as said substituents, alkoxy group that may also be substituted by 1-3 halogen atoms (for example, fluorine, chlorine, bromine, and iodine) (for example, C_{1-4} alkoxy such as methoxy, ethoxy, and propoxy, halogen-C_{1-4} alkoxy such as trifluoromethoxy, pentafluoroetohxy, and 2,2,2-trifluoroethoxy), halogen atom (for example, fluorine, chlorine, bromine, and iodine), alkyl group that may also be substituted by 1-5 halogen atoms (for example, fluorine, chlorine, bromine, and iodine) (for example, C_{1-4} alkyl such as methyl, ethyl, and propyl, trifluoromethyl, pentafluoroethyl, 2,2,2-trifluoroethyl, aryl group (for example, C_{6-10} aryl such as phenyl, 1-naphthyl, and 2-naphthyl), cyano group, nitro group, etc., are mentioned.

[0018] The condensed benzene derivative represented by the general formula (I) of the present invention may form a salt, and as said, acid added salts such as inorganic acid salt (for example, hydrochloride, sulfate, hydrobromate, phosphate, etc.), organic acid salt (for example, acetate, trifluoroacetate,

succinate, maleate, fumarate, propionate, succinate, tartrate, malate, lactate, oxalate, methanesulfonate, p-toluenesulfonate, etc.), etc., and salts with bases (for example, alkali metal salt such as potassium salt, sodium salt, and lithium salt, alkaline-earth metal salt such as calcium salt and magnesium salt, and salts with organic bases such as ammonium salt, trimethylamine salt, triethylamine salt, tert-butyldimethylamine salt, dibenzylmethylamine salt, benzyldimethylamine group, N,N-dimethylaniline salt, pyridine salt, and quinoline salt) may also be formed. Also, the condensed benzene derivative represented by the general formula (I) or its salt may be a hydrate. Hereinafter, these salts and hydrates are called compound (I). The compound (I) of the present invention has one or more asymmetric carbons in the molecule, and any of R arrangement and S arrangement for these asymmetric carbons is included in the present invention. The compound (I) is manufactured by the following methods, for instance. Next, it s reaction equation is shown in the figure, and each symbol of the compounds in the following schematic diagram show the same meaning as the above-mentioned one. Also, all of compounds (Ia), (Ib), (Ic), and (Id) that will be mentioned later are compounds being included in the compound (I) of the present invention. A raw material compound and a synthesis intermediate

may be used as salts similar to the compound (I) in addition to a free body, and a reaction mixed solution may be provided as it is to the reaction or may also be provided after being isolated by a well-known means.

(Structure 9)

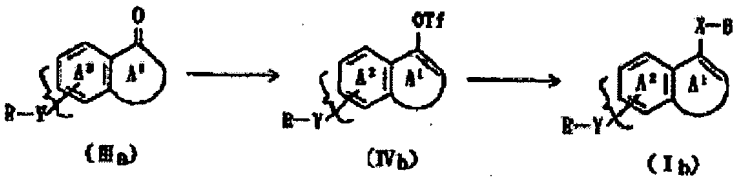


/8

First, a compound (IVa) is synthesized by sending a ketone compound (IIIa) to a reduction reaction. As a reducing agent being used, for example, sodium boron hydride, lithium aluminum hydride, tri-t-butoxy aluminum lithium hydride, tri-sec-butyl boron lithium hydride, etc., are used. The amount of reducing agent being used is usually about 1-4 moles, preferably about 1 mole to 1 mole compound (IIIa). This reaction is favorably carried out using an inactive solvent to the reaction. As long

as the reaction is advanced using such a solvent, though there is no particular limitation, for example, ethers such as tetrahydrofuran, hydrocarbon halide such as dichloromethane, alcohols such as methanol, and hydrocarbons such as hexane and toluene are preferable. The reaction time depends on the activity and the amount of reducing agent being used, however it is usually 30 min-24 h, preferably 30 min-10 h. The reaction temperature is usually -78°C to 30°C. Then, a compound (IIa) can be synthesized by reacting the compound (IVa) and a reagent such as thionyl chloride, trifluoromethanesulfone anhydride, and carbonyldiimidazole. The amount of reagent being used is usually about 1-5 mole to 1 mole compound (IVa). As the solvent being used in this reaction, for example, ethers such as tetrahydrofuran, hydrocarbon halide such as dichloromethane, etc., are mentioned. The reaction time is usually 1-24 h. The reaction temperature is usually -78°C to 30°C. Then, a compound (Ia) can be synthesized by reacting the compound (IIa) and an XB. The amount of XB being used is about 1-10 mole to 1 mole compound (IIa). This reaction is usually carried out using an inactive solvent to the reaction. As such a solvent, for example, ethers such as N,N-dimethylformamide and tetrahydrofuran, hydrocarbon halide such as dichloromethane, etc., are mentioned. The reaction time is usually 1-24 h.

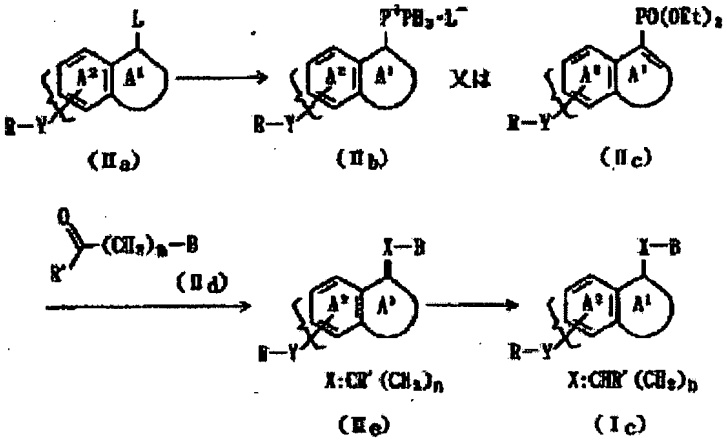
(Structure 10)



A compound (IVb)(in the formula, Tf shows trifluoromethanesulfonyl) is synthesized by reacting the compound (IIIa) with trifluoromethanesulfonic anhydride in the presence of a base. The amount of trifluoromethanesulfonic anhydride being used is usually about 1-3 mole to 1 mole compound (IIIa). As the solvent being used in this reaction, for example, hydrocarbon halide such as cyclomethane, ethers such as tetrahydrofuran, etc., are mentioned. As the base, for example, diisopropylethylamine, 2,6-di-tert-butylpyridine, 2,6-di-tert-butyl-4-methylpyridine, etc., are mentioned. The amount of base being used is usually 1-10 mole to 1 mole compound (IIIa). The reaction temperature is usually -78°C to 30°C. Then, a compound (Ib) can be synthesized by sending the compound (IVb) to a nucleophilic substitution reaction or a carbon-carbon bond generation reaction using a transition metal such as palladium. This reaction can be carried out by a well-known

method described in Journal of Medical Chemistry (J. Med. Chem.), Vol. 38, pp.2463-2471 (1995), etc., or a method based upon it.

(Structure 11)



/9

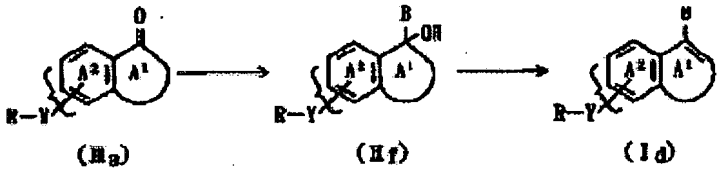
First, compounds (IIb) and (IIc) are synthesized by treating a compound (IIa) with triphenylphosphine or triethyl phosphate. Then, a compound (IIe) can be synthesized by a Wittig type reaction (for example, Wittig reaction, Horner-Emonds reaction, etc.) of the compound (IIb) or (IIc) and a compound (IId) (R′ represents a hydrogen or lower alkyl). This

reaction can be carried out by a well-known methods such as a method described in Berichte. 87, 1318 (1954) or a method based upon it.

[0019] Then, a compound (Ic) can be synthesized by sending the compound (IIa) to a reduction reaction. Said reduction reaction is carried out without a solvent or in an appropriate solvent in the presence of a contact reducing agent and hydrogen. The contact reducing agent is usually 0.01-500 wt%, preferably about 0.01-250 wt% to 1 mole compound (IIe). As the contact reducing agent, palladium black, palladium carbon, platinum oxide, platinum black, Raney nickel, Raney nickel, etc., are mentioned. This reaction is favorably carried out using an inactive solvent to the reaction. As such a solvent, there is no particular limitation as long as the reaction is advanced, however for example, alcohols such as methanol, ethanol, and propanol, ethers such as diethyl ether, tetrahydrofuran, dioxane, and 1,2-dimethoxyethane, hydrocarbons such as benzene, toluene, and cyclohexane, amides such as N,N-dimethylformamide and N,N-dimethylacetamide, nitriles such as acetonitrile and propionitrile, esters such as ethyl acetate, organic acids such as formic acid and acetic acid, etc., are used. They are used alone or as a mixed solvent of two kinds or more. The reaction time is usually 0.5-24 h, preferably 0.5-5 h, though it depends

on the activity and the amount of reducing agent being used. The reaction temperature is usually 0-120°C, preferably 10-70°C.

(Structure 12)



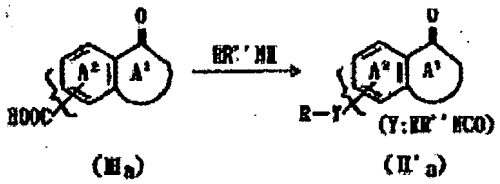
First, a compound (IIf) is synthesized by sending a ketone compound (IIIa) along with a nucleating agent into an appropriate solvent to 1,2 addition reaction. As the nucleating agent, for example, an organic metal compound (for example, Grignard reagent, organolithium reagent, etc.) is used. The amount of nucleating agent being used is usually 1-5 moles to 1 mole compound (IIIa). As the solvent being used in the present invention, for example, ethers such as tetrahydrofuran and dimethoxyethane, hydrocarbons such as hexane and toluene, hydrocarbon halides such as dichloromethane, etc., are mentioned. The reaction time is usually 1-24 h. The reaction temperature is usually -78°C to 30°C. Then, a compound (Id) can be synthesized by sending a compound (IIf) to a dehydration reaction. This reaction can be carried out using sulfuric acid

along with a solvent, for example, organic acids such as acetic acid and hydrocarbons such as toluene.

The reaction temperature is in a range of 0°C to the boiling point of the solvent, however it is generally 0-100°C.

[0020]

(Structure 13)

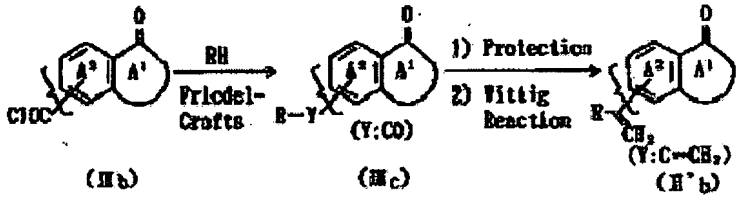


A ketone compound (II'a) as a starting material can be synthesized by a well-known reaction. For example, in case Y is an amide bond (II'a), a carboxylic acid or a reactive derivative (IIIa) of carboxylic acid (for example, it can be synthesized by condensing activated esters such as mixed acid anhydride, carbonylimidazole, and phenyl ester) in the presence of an amine compound RR"NH (R" represents hydrogen and lower alkyl) and a base (for example, tertiary amine such as pyridine, dimethylaminopyridine, triethylamine, and diisopropylethylamine, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, etc.). At that time, in the reaction of

carboxylic acid and amine, a condensing agent (for example, carboimides such as dicyclohexylcarbodiimide, phosphorus compound such as diethyl phosphate, diphenylphosphoric acid, BOP chloride, and phosphorus trichloride, etc.) is appropriately used. The amount of amine compound RR"NH being used is usually about 1-5 mole, preferably about 1-2.0 mole to 1 mole compound (IIIa). This reaction is favorably carried out using an inactive solvent to the reaction. As such a solvent, there is no particular limitation as long as the reaction is advanced, however for example, ethers such as diethyl ether, tetrahydrofuran, dioxane, and 1,2-dimethoxyethane, hydrocarbons such as benzene, toluene, and cyclohexane, amides such as N,N-dimethylformamide and N,N-dimethylacetamide, hydrocarbon halides such as dichloromethane, chloroform, carbon tetrachloride, and 1,2-dichloroethane, and nitriles such as acetonitrile and propionitrile are preferably used as a solvent or a mixed solvent. In case an acid halide is used as the reactive derivative of carboxylic acid, the reaction can be carried out in the presence of an deoxidizer for the purpose of removing a hydrogen halide being discharged from the reaction system. As such a deoxidizer, for example, inorganic base such as sodium carbonate, potassium carbonate, and sodium hydrocarbon, aromatic amines such as pyridine and lutidine, tertiary amines such as

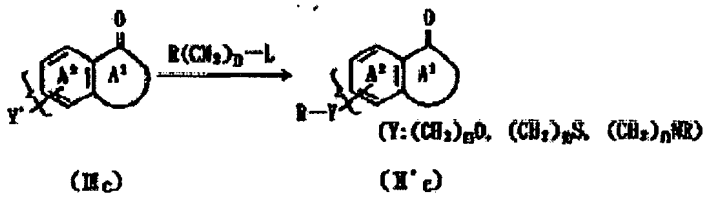
triethylamine, tripropylamine, tributylamine, cyclohexyldimethylamine, 4-dimethylaminopyridine, N,N-dimetnylaniline, N-methylpiperidine, N-methylpyrrolidine, and N-methylmorpholine are preferably used. The reaction time is usually 30 min-24 h, though it depends on the reagent or solvent being used. The reaction temperature is usually 0-100°C, preferably 0-70°C.

(Structure 14)



According to the method described in Chemical and Pharmaceutical Bulletin, 26, 1776 (1978), a compound (IIIc) in which Y is a carbonyl group can be synthesized by sending a reactive derivative of a carboxyl group such as (IIIb) and RH to the Fricdel-Crafts reaction. The reaction is carried out in the presence of 1-5 mole Lewis acid (for example, aluminum chloride, aluminum bromide, tin chloride, antimony chloride, titanium chloride, boron trifluoride, sulfuric acid, etc.) to 1 mole

compound (IIIb). At that time, the solvent being used is not particularly limited as long as it is inactive to the reaction, and for example, carbon disulfide, hydrocarbon halide, etc., are commonly used. A reaction matrix such as benzene and toluene may also be used as it is as a solvent. The reaction temperature is in a range of 0°C to the boiling point of the solvent, and 20-80°C is generally adopted. Furthermore, a compound (II'b) of alkylidene can be synthesized by sending a compound (IIIc) to the above-mentioned Wittig type reaction. (Structure 15)



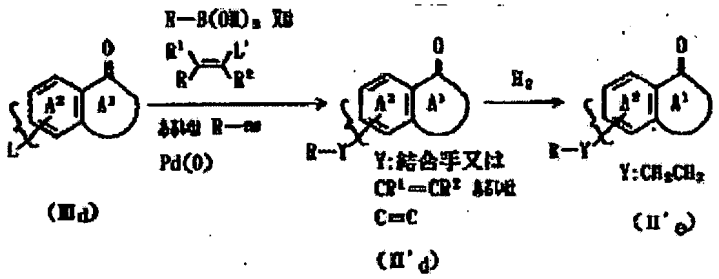
(IIIc) (II'c)

In case the bond (II'c) (n represents 0 or 1), if n is 0, a compound (IIIC) having amino, hydroxy, and thiol group (Y' represents amino group, hydroxy group, and thiol group) is sent to the Ullmann reaction (Ann. 332, 38 (1904)) in the presence of bromobenzenes and a copper catalyst according to the method described in Chemical and Pharmaceutical Bulletin, 26, 2475 (1978), or the reaction with diphenyl iodonium chlorides is

carried out, so that a compound (II'c) in which Y is $NR(CH_2)n$, $O(CH_2)n$, or $S(CH_2)n$ (in the formula, Y represents $CH_2)nO$, $CH_2)nS$, or$(CH_2)nNR$) can be synthesized. A compound (II'c) in which n is 1 can be synthesized by applying an alkylation reaction to a compound R(CH2)n-L in the presence of a base (for example, tertiary amine such as pyridine, dimethylaminopyridine, trimethylamine, and diisopropylethylamine, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, /11 sodium hydroxide, etc.).

[0021]

(Structure 16)



1. Or

2. Y: Coupler or $CR^1=CR^2$ or C≡C

A compound (II'd) in which Y is a coupler can be synthesized by a method described in Grignard reaction (for example, Competes Rendus, 130, 1322 (1900) or a method based upon it), a carbon-carbon bond generation reaction (for example, a method described in Precision Organic Synthesis (experimental manual), revised 2nd edition, pp.214-223 or a method based upon it) using a transition metal (for example, Heck reaction using a palladium catalyst, Suzuki reaction, etc.), etc., by a compound (IIId)

(Structure 17)

$R\text{-}B(OH)_2$ or 

(L' represents a hydrogen or lower alkyl, and R^1 and R^2 represent a lower alkyl) or R-≡. Similarly, a compound (II'd) in which Y is $-CR^1\text{-}CR^2$ or -C≡C- can be synthesized by applying the carbon-carbon bond generation reaction using ethylene or acetylene and a transition metal (for example, Heck reaction (Journal of Organic Chemistry, 37, 2320 (1972), Suzuki reaction (Tetrahydron 1994, 50, 2003) using a palladium catalyst) to a compound (IIId). Then, a compound (II'e) in which Y is $CR^1\text{-}CR^2$ or -C≡C-

can be synthesized by a hydrogenation reaction according to an ordinary method. If an intended product is obtained in an isolated state by the above-mentioned reaction, it can also be converted into an isolated body or other salts by an ordinary method. The compound (I) being obtained in this manner can be isolated and purified from the reaction solution by a well-known method such as transfer dissolution, enrichment, solvent extraction, distillation, crystallization, recrystallization, chromatography, etc. Also, in the above-mentioned each reaction, a protective may also be used for the amino group, carboxyl group, and hydroxy group irrelevant to the above-mentioned each reaction, and the protective group can be added and removed by well-known means.

[0022] As the protective group of the amino group, for example, formyl, C_{1-6} alkylcarbonyl (for example, acetyl, propionyl, etc.), phenylcarbonyl, C_{1-6} alkyl-oxycarbonyl (for example, methoxycarbonyl, ethoxycarbonyl, etc.), phenyloxycarbonyl, C_{7-10} alkyloxy-carbonyl (for example, phenyl-C_{1-4} alkyloxy-carbonyl such as benzyloxycarbonyl, etc.), trityl, phthaloyl, or N,N-dimethylaminomethylene, etc., which may respectively have substituents are used. As these substituents, halogen atom (for example, fluorine, chlorine, bromine, iodine, etc.), formyl, C_{1-6} alkyl-carbonyl (for example, acetyl, propionyl, varelyl, etc.),

nitro group, etc., are used, and the number of substituents is about 1-3 pieces. As the protective group of the carboxyl group, for example, C_{1-6} alkyl (for example, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, trityl, or sylyl which may respectively have substituents are used. As these substituents, halogen atom (for example, fluorine, chlorine, bromine, iodine, etc.), formyl, C_{1-6} alkyl-carbonyl (for example, acetyl, propionyl, varelyl, etc.), nitro group, etc., are used, and the number of substituents is about 1-3 pieces

[0023] As the protective group of the hydroxy group, for example, C_{1-6} alkyl (for example, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, etc.), phenyl, C_{7-10} aralkyl (for example, phenyl-C_{1-4} alkyl such as benzyl, etc.), formyl, C_{1-6} alkyl-carbonyl (for example, acetyl, propionyl, etc.), phenyloxycarbonyl, benzoly, (C_{7-10} aralkyloxy)carbonyl (for example, phenyl-C_{1-4} alkyloxy-carbonyl such as benzyloxycabonyl, etc.), pyranyl, furanyl, or sylyl which may respectively have substituents can be used. As these substituents, halogen atom (for example, fluorine, chlorine, bromine, iodine, etc.), formyl, C_{1-6} alkyl (for example, methyl, ethyl, propyl, etc.), phenyl, C_{7-10} aralkyl (for example, phenyl-C_{1-4} alkyl such as benzyl, etc.), nitro group, etc., are used, and the number of

substituents is about 1-4 pieces. Also, as a method for removing the protective group, a well-known method or a method based upon it is employed, and for example, a treatment method using acid, base, reduction, ultraviolet rays, hydrazine, phenylhydrainze, sodium N-methyldithiocarbamate, tetrabutyl ammonium fluoride, palladium acetate, etc., is employed. /12 Also, in case the compound (I) exists as diastereomer, conformer, etc., if desired, they can be isolated by the above-mentioned separation and purification means. Also, in case the compound (I) is a racemic body, it can be separated into d body and l body by an ordinary optical split means. In case the compound (I) includes a basic group, it can be changed to an acid added salt by a well-known method.

[0024] The compound (I) of the present invention has excellent effects as a medicine and has an excellent inhibition activity, especially to a steroid C_{17-20} lyase. Since the compound (I) has low toxicity and little side effect, it is useful to treating and preventing medicine for various kinds of diseases, for example, (1) cancers of malignant tumors (for example, prostatic cancer, breast cancer, uterine cancer, ovary cancer, stomach cancer, etc.) and their transfer and regeneration, (2) symptoms due to these cancers (for example, pain, poor liquid quality, etc.), (3) prostatic hypertrophy masculinization,

hypertrichosis, breast cancer, uterine cancer, mastitis, hysteromyoma, endometriosis, etc., for mammal animals (for example, human beings, cows, dogs, cats, monkeys, mice, rats, etc., especially human beings). The compound (I) of the present invention exhibits excellent effects, even if it is used alone, however with the combination with other medical formulations and therapeutic methods, its effects can be further reinforced. As the agents being used together, for example, sex hormone, alkylating agent, antimetabolite, anticancer antibiotic, plant alkaloid, immunotherapeutic agent, etc., are mentioned, however the agents are not limited to them. As the sex hormone, for example, phosfesterol, diethylstylylbestrol, chlorotrianicene, medroxyprogesterone acetate, megestrol acetate, chloromasinone acetate, ciproterone acetate, antiestrogen (for example, tamoxyphene citrate, tremiphene citrate, etc.), mepithiostan, testrolactone, amynoglutimide, LH-RH agonist (for example, gocelelin acetate, bucelelin, ryuprorelin, etc.), dororoxyphene, epithiostanol, ethynylestradiol sulfoante, LH-RH antagonist (for example, cetrorelix, ganirelix, azalin B, etc.), aromatase inhibitor (for example, fadorosole chlorate, anastrosole, retrosole, excemestan, borosole, phormestan, etc.), 5α-reductase inhibitor (for example, finasteride, etc.), antiantrogen agent (for example, furtamide, bicartamide, etc., retinoid, and agent

for delaying the metabolism of retinoid (for example, rearozole, etc.), etc., are mentioned.

[0025] As the alkylating agent, for example, nitrogen mustard, nitrogen mustard-N-oxide, chlorambutyl, cyclophosphamide, iphosphamide, tioteba, carbocon, inprosulphane tocylate, busulphane, nimstin chlorate, mitobronitol, merphalane, dacalbazine, lanimstin, estramstin sodium phosphate, trietylenemelaine, calmstin, romstin, streptomycin, pipobroman, etoglucide, carboplatin, cisplatin, miboplatin, nedaplatin, oxariplatin, althretamin, anbamstin, dibrospdium chlorate, fotemstin, predonimstin, pumitepa, ribomstin, temozoromide, threosulfane, torophosphamide, dinostatinstyram, etc., are mentioned. As the antimetabolite, for example, mercaptopurin, thioinosine, metothrexato, enosintabin, citarabin, citarabinocphosphate, ancitambin chlorate, 5-FU system drug (for example, fluorourasil, degaful, UFT, doxyflouridin, carmoful, flutsuron, neofluron, etc.), aminoputeiln, leucopolin calcium, tabroid, butosin, forineto calcium, reboforineto calcium, cradoribin, emitepul, puldarabin, damutabin, hydroxycarbamide, pentstatin, etc., are mentioned.

[0026] As the anticancer antibiotic, for example, actimycin D, actinomycin C, maitomycin C, cromomycin A_3, bureomycin chlorate, breomycin sulfate, pepromycin sulfate, daunobisin, acralbirin

chlorate, pyralbisin chlorate, epichlopyricin chlorate, neocathinostantin, mirastmycin, salcomycin, caltinophyrin, mitotan, sorbisin chlorate, mitoxantron chlorate, etc., are mentioned. As the plant alkanoid, for example, etpoxide, etopoxide phosphate, binplastin suflate, bincrystin sulfate, bindesin sulfate, deniposide, pacritaxicel, binorurebin, etc., are mentioned. As the immunotherapeutic agent (BRM), for example, picivanyl, crestin, cisofilane, retinan, ubenimecus, interferon, interleukin, microphage colony stimulant factor, granular colony stimulant factor, erysropoethin, rinphosin, BCG vaccine, corinebactrium, palibum, rebamisol, polysaccharide K. prokotasole, etc., are mentioned. In adiditon, L-asparaginase, acedalactone, procarbacin chlorate, doxisorbin, protoporphin, cobalt complex salt, mercury hematporphin sodium, topoisomerase I inhibitor (for example, irinodecan, etc.), topoisomerase II inhibitor, differentiation inducing drug (for example, retinoid, vitamin D, etc.), multiplication factor inhibitor (for example, sramin, etc.), α-blocker (for example, tamstrocin chlorate, etc.), blood vessel generation inhibitor, etc., can also be used. Also, along with the chemotherapeutic method for dosing the compound (I) of the present invention, for example, surgery, hydrothermal therapy, radiotherapy, etc., can also be employed in combination. /13

[0027] As medically allowable carriers, various kinds of ordinary organic or inorganic carriers as formulation materials are used. Excipient, lubricant, binder, disintegrator, and tackifier in solid formulations; solvent, dispersant, dissolution aid, suspension agent, isotonic agent, buffer agent, painkiller, etc., in liquid formulations, etc., are mixed at an appropriate amount. Also, if necessary, additives such as antiseptic, antioxidant, colorant, and sweetener can be used. As appropriate examples of the excipient, lactose, white sugar, D-mannitol, starch, crystal cellulose, light silicic anhydride, etc., are mentioned. As appropriate example of the lubricant, magnesium stearate, calcium stearate, talc, colloidal silica, ec., are mentioned. As appropriate examples of the binder, crystal cellulose, white sugar, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropymethyl cellulose, polyvinylpyrrolidone, etc., are mentioned. As appropriate examples of the disintegrator, starch, carboxymethyl cellulose, carboxymethyl cellulose, cross carmerose sodium, carboxymethyl starch sodium, etc., are mentioned. As appropriate examples of the tackifier, natural gums, cellulose derivative, acrylic acid polymer, etc., are mentioned. As appropriate examples of the solvent, water for injection, alcohol, propylene glycol, makugol, sesame oil, corn oil, etc., are mentioned. As

appropriate examples of the dispersant, Tween 80, HCO 60, polyethylene glycol, carboxymethyl cellulose, sodium alginate, etc., are mentioned. As appropriate examples of the dissolution aid, polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc., are mentioned. As appropriate examples of the suspension agent, surfactant such as stearyltriethanolamine, sodium laurylsulfate, laurylaminopropionic acid, recitin, benzalconium chloride, benzetonium chloride, and glycerin monostearate; hydrophilic polymer such as polyvinyl alcohol, polyvinylpyrrolidone, carboxymethyl cellulose sodium, methyl cellulose, hydroxymethyl cellulose, hyroxyethyl cellulose, and hydroxypropyl cellulose, etc., are mentioned. As appropriate examples of the isotonic agent, sodium chloride, glycerin, D-mannitol, etc., are mentioned. As appropriate examples of the buffer agent, buffer solution such as phosphate, acetate, carbonate, citrate, etc., are mentioned. As appropriate examples of the painkiller, benzyl alcohol, etc., are mentioned. As appropriate examples of the aseptic, paraoxybenzoic acid esters, chlorophthalol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid, etc., are mentioned. As appropriate examples of the antioxidant, sulfite, ascorbic acid, etc., are mentioned.

[0028] The medical drug of the present invention can be manufactured according to an ordinary method, and the content ratio of the compound (I) in formulations is usually 0.1-100% (w/w). Detailed examples are shown below.

(1) Tablet, powder, granule, and capsule: for example, excipient, disintegrator, binder, or lubricant are added to the compound (I), and if necesdary, masking of a taste and coating for enteric coating or retention can be applied.

(2) Injection agent: The compound (I) along with dispersant, preservative, isotonic agent can be dissolved as an aqueous injection agent in plant oil such as olive oil, sesame oil, cottonseed oil, and corn oil, propylene glycol, etc., suspended or emulsified, and molded as an injection agent.

(3) Suppository: The compound (I) is manufactured by changing the composition (I) into an oily or aqueous solid, semi-solid, or liquid composition. As an oil base agent being used in this composition, for example, glyceride (for example, cacao fat, wintepsols, etc.) of higher fatty acid, intermediate fatty acid (for example, mygriols, etc.), or plant oil (for example, sesame oil, soybean oil, cottonseed oil, etc.), etc., are mentioned. As the aqueous gel base agent, for example, natural gums, cellulose derivative, vinyl polymer, acrylic acid polymer, etc., are mentioned. The mixture ratio of the compound (I) in these

formulations is usually 0.01-50%, though it depends on the kind of formulation.

[0029] The amount of compound of the present invention being used in the above-mentioned medical formulations depends on the compound being selected, the animal species being selected for dosage, its dosage times, etc., however its effectiveness is exerted over a wide range. For example, for adult solid tumor patients (for example, prostatic cancer patients), if the medical formulation of the present invention is orally dosed, the amount of dose a day is usually about 0.001-500 mg/kg weight, preferably about 0.1-40 mg/kg weight, and more preferably about 0.5-20 mg/kg weight as an effective amount of compound (I) of the present invention. However, if it is parenterally dosed or other anticancer agents used, the amount of dose is smaller than that. However, the amount of compound being actually dosed is determined by the selection of the compound, various kinds of formulation shapes, patient age, weight, and sex, degree of disease, dosage path, dosage period and interval, etc., and the amount can be changed at any time by the decision of a doctor. The dosage path of the above-mentioned medical formulation is not particularly limited by various situations, and for example, it can be orally or parenterally dosed. Here, "parenteral" being used includes the

dosage into vein, muscle, skin, nose cavity, eye, brain, direct intestines, abdominal cavity, etc. The dosage period and interval of the abovementioned medical formulation depend on /14 various situations and are decided at any time by the decision of a doctor, and there are split dosage, continuous dosage, intermittent dosage, short-term large-amount dosage, and repetitive dosage methods. For example, in an oral dosage, the formulation is preferably dosed by spitting it into one or several times (especially 1-3 times a day) a day. Also, it can be dosed as a slow-release formulation and can also be dripped in the vein for a long time.

[0030]

(Embodiments of the invention)

The present invention is further explained in detail by the following application examples, formulation examples, and test examples, however these examples are simple applications and do not limit the present invention. Also, they may be modified in the range where the range of the present invention is not deviated. Abbreviations in the application examples have the following meanings.

s: Singlet, d: Doublet, t: triplet, q: Quartet, dd: Double doublet, dt: Double triplet, m: Multiplate, br: Wide, J:

Coupling constant, Room temperature: 0-30°C, DMF: N,N-dimethylformamide, THF: Tetrahydrofuran

Formulation Example 1

Capsule:

(1) Compound obtained in Application Example 5 10 mg

(2) Lactose 90 mg

(3) Microcrystalline cellulose 70 mg

(4) Magnesium stearate 10 mg

1 capsule 180 mg

The total amount of said (1), (2), and (3) and 5 mg of (4) were kneaded and granulated, and 5 mg of the remaining (4) was added to it. The entire part was sealed into a gelatin capsule.

[0031] Formulation Example 2

Tablet:

(1) Compound obtained in Application Example 5 10 mg

(2) Lactose 35 mg

(3) Corn starch 150 mg

(4) Microcrystalline cellulose 30 mg

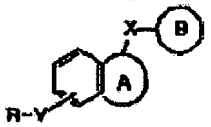
(5) Magnesium stearate 5 mg

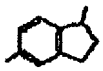
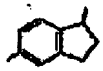
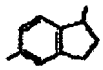
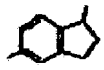
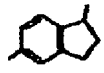
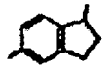
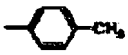
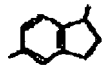
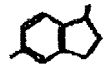
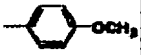
1 tablet 230 mg

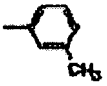
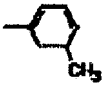
The total amount of said (1), (2), and (3) and 20 mg of (4) were kneaded and granulated, and 10 mg of the remaining (4) and 2.5 mg of (5) were added to the granule and molded under pressurization, so that a tablet was formed.

[0032]

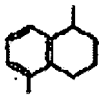
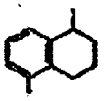
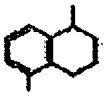
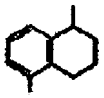
(Table 1)



実施例	A	X	B	Y	R	塩
1		OCO		結合		
2		結合		結合		
3		結合		結合		HCl
4		結合		結合		
5		結合		結合		フマル酸
6		結合		結合		
7		結合		結合		フマル酸
8		結合		結合		
9		結合		結合		フマル酸
10		結合		結合		
11		結合		結合		フマル酸
12		結合		結合		
13		結合		結合		フマル酸

実施例	A	X	B	Y	R	塩
14		結合		O		
15		結合		O		
16		結合		O		フマル酸
17		結合		O		
18		結合		O		フマル酸
19		結合		O		
20		結合		O		フマル酸
21		結合		O		
22		結合		O		フマル酸
23		結合		O		
24		結合		O		フマル酸

実施例	A	X	B	Y	R	塩
25		結合		CO		
26		結合		CO		フマル酸
27		結合		CO		
28		結合		CO		フマル酸
29		結合		CO		
30		結合		OCH_2		
31		結合		OCH_2		フマル酸
32		結合		OCH_2		
33		結合		OCH_2		
34		結合		OCH_2		フマル酸
35		結合		OCH_2		

実施例	A	X	B	Y	R	塩
36		結合		OCH_3		
37		結合		OCH_2		
38		結合		OCH_2		
39		結合		O		
40		結合		OCH_2		

1. Application Example

2. Bond

3. Fumaric acid

[0033]

(Application examples)

Application Example 1

Manufacture of 5-cyclohexyl-1-(1H-imidazole-1-ilucarbonyloxy)indane:

1,1-carbonyldimidazole (953 mg) was added to a tetrahydrofuran (20 mL) solution of 5-cyclohexyl-1-indanol (1.0 g) being obtained by a method described in J. Med. Chem., 15, 1297 (1972), and the reaction solution was refluxed for 2 h. The reaction solution was diluted with dichloromethane, washed with water and a saline solution, and dried, and the solvent was distilled off, so that a colorless solid 5-cyclohexyl-1-(1H-imidazole-1-ilucarbonyloxy)indane (1.44 g) was obtained.

^{1}H-NMR ($CDCl_3$)δ: 1.20-1.53 (6H, m), 1.65-1.95 (4H, m), 2.31 (1H, m), 2.45-2.70 (2H, m), 2.92 (1H, m), 3.18 (1H, m), 6.38 (1H, dd, J=2.8, 6.6 Hz), 7.04 (1H, t, J=1.4 Hz), 7.04-7.20 (2H, m), 7.40 (1H, t, J=1.4 Hz), 7.44 (1H, d, J=8.0 Hz), and 8.11 (1H, s)

Application Example 2

Manufacture of 5-cyclohexyl-1-(1H-imidazole-1-yl)indane:

Imidazole (2.67 g) and oily sodium hydride (20 mg) were added to N,N-dimethylformamide (15 mL) solution of 5-cyclohexyl-1-(1H-imidazole-1-ilcarbonyloxy)indane (1.29 g) and stirred at 100°C for 2 h. The reaction solution was enriched, and the residue was dissolved in ethyl acetate, washed with water and a saline solution, and dried, and the solvent was distilled off. The residue was purified by a silica gel column chromatography (dichloromethane:methanol = 30:1), so that a wax-shaped 5-cyclohexyl-1-(1H-imidazole-1-yl)indane (569 mg) was obtained.

^{1}H-NMR ($CDCl_3$)δ: 1.20-2.00 (10H, m), 2.18 (1H, m), 2.51 (1H, m), 2.68 (1H, m), 2.85-3.20 (2H, m), 5.62 (1H, t, J=7.0 Hz), 6.83 (1H, t, J=1.2 Hz), 6.98-7.12 (3H, m), 7.18 (1H, s), and 7.51 (1H, s)

[0034] Application Example 3

Manufacture of 5-cyclohexyl-1-(1H-imidazole-1-yl)indane·carbonate:

2 N ethyl acetochlorate solution (10 mL0 was added to an ethyl acetate solution of 1-(1H-imidazole-1-yl)-5-phenylindane (528 mg), and the crystal generated was filtered, washed with ether, and dried, so that a colorless crystal 5-cyclohexyl-1-(1H-imidazole-1-yl)indane·carbonate (125 mg) was obtained.

^{1}H-NMR ($CDCl_3$)δ: 1.20-2.00 (10H, m), 2.25 (1H, m), 2.55 (1H, m), 2.83 (1H, m), 3.00-3.20 (2H, m), 5.93 (1H, dd, J=4.0, 7.0 Hz), 7.04 (1H, t, J=1.6 Hz), 7.10-7.20 (2H, m), 7.24 (1H, s), 7.40 (1H, s), and 8.66 (1H, s)

[0035] Application Example 4

Manufacture of 1-(1H-imidazole-1-yl)-5-phenylindane:

2 M aqueous sodium carbonate solution (10 mL) was added to a mixture of 5-bromo-1-indanone (2.11 g), phenylboric acid (1.586 g), tetrakistriphenylphosphine palladium (0) (1.0 g), and dimethoxyethane (30 mL), and the reaction solution was refluxed for 15 h. The reaction solution was diluted with ethyl acetate, and the organic layer was washed with water and a saline solution and dried. The solvent was distilled off, and the residue was purified by a silica gel column chromatography (hexane:dichloromethane:ethyl acetate = 10:2:1) and recrystallized from cyclohexane, so that a colorless crystal 5-phenyl-1-indanone (1.664 g) was obtained.

^{1}H-NMR ($CDCl_3$)δ: 2.75 (2H, t, J=5.8 Hz), 3.21 (2H, t, J=5.8 Hz), /19 7.39-197.52 (3H, m), 7.57-7.70 (4H, m), and 7.83 (1H, d, J = 7.8 Hz)

Sodium boron hydride (183 mg) was added to methanol (10 mL)-tetrahydrofuran (5 mL) solution of 5-phenyl-1-indanone (1.0 g), and the reaction solution was stirred for 30 min. The

reaction solution was enriched, and the residue was dissolved in ethyl acetate, washed with water and a saline solution, and dried. The solvent was distilled off, and the residue was sent by a silica gel column chromatography (ethyl acetate) and rerystallized from cyclohexane, so that a colorless crystal 5-phenyl-1-indanol (997 mg) was obtained.

^{1}H-NMR ($CDCl_3$)δ: 2.02 (1H, m), 2.55 (1H, m), 2.89 (1H, m), 3.13 (1H, m), 5.30 (1H, dd, J=5.2, 7.0 Hz), 7.30-7.50 (6H, m), and 7.53-7.62 (2H, m)

Dichloromethane (2 mL) solution of thionyl chloride (2.03 g) was dropped into a dichloromethane (20 mL) solution of 5-phenyl-1-indanol (897 mg) and refluxed for 1 h after dropping. The reaction solution was enriched, and the residue was dissolved in DMF (25 mL). Imidazole (2.90 g) was added to it and stirred at 100°C for 2 h. The reaction solution was enriched, and the residue was dissolved in ethyl acetate, washed with water and a saline solution, and dried. The solvent was distilled off, and the residue was purified by a silica gel column chromatography (dichloromethane:methanol = 50:1), so that a wax-shaped 1-(1H-imidazole-1-yl)-5-phenylindane (578 mg) was obtained.

^{1}H-NMR ($CDCl_3$)δ: 2.28 (1H, m), 2.76 (1H, m), 3.01 (1H, m), 3.20 (1H, m), 5.72 (1H, t, J=7.0 Hz), 6.89 (1H, s), 7.10 (1H,

s), 7.18 (1H, d, J = 8.0 Hz), 7.30-7.50 (4H, m), and 7.53-7.65 (4H, m).

[0036] Application Example 5

Manufacture of 1-(1H-imidazole-1-yl)-5-phenylindane·fumarate

A methanol solution of fumaric acid (232 mg) was added to an ethyl acetate solution of 1-(1H-imidazole-1-yl)-5-phenylindane (578 mg), and the solvent was enriched. The residue was crystallized from ethyl acetate ether, filtered, washed with ether, and dried, so that a colorless crystal 1-(1H-imidazole-1-yl)-5-phenylindane·fumarate (642 mg) was obtained.

^{1}H-NMR (DMSO-d_6)δ: 2.26 (1H, m), 2.70 (1H, m), 3.00 (1H, m), 3.20 (1H, m), 5.78 (1H, t, J=7.3 Hz), 6.62 (2H, s), 6.94 (1H, s), 7.10 (1H, d, J=7.8 Hz), 7.12 (1H, s), 7.30-7.53 (4H, m), 7.60-7.70 (3H, m), and 7.80 (1H, s)

Next, the compounds of Application Examples 6-13 were synthesized by methods similar to Application Examples 4 and 5.

Application Example 6

5-(4-fluorophenyl)-1-(1H-imidazole-1-yl)indane

^{1}H-NMR ($CDCl_3$)δ: 2.27 (1H, m), 2.76 (1H, m), 2.93-3.27 (2H, m), 5.71 (1H, t, J=7.1 Hz), 6.87 (1H, t, J=1.2 Hz), 7.09 (1H, s), 7.10-7.20 (3H, m), 7.41 (1H, dd, J=1.6, 8.0 Hz), and 7.48-7.60 (4H, m).

[0037] Application Example 7

5-(4-fluorophenyl)-1-(1H-imidazole-1-yl)indane·fumarate

^{1}H-NMR (DMSO-d_6)δ: 2.22 (1H, m), 2.68 (1H, m), 3.02 (1H, m), 3.23 (1H, m), 5.86 (1H, t, J=7.1 Hz), 6.62 (2H, s), 6.94 (1H, s), 7.09 (1H, d, J=8.0 Hz), 7.12 (1H, s), 7.29 (2H, t, J=8.8 Hz), 7.48 (1H, dd, J=1.6, 8.0 Hz), and 7.78 (1H, s)

Application Example 8

1-(1H-imidazole-1-yl)-5-(4-methylphenyl)indane·fumarate

^{1}H-NMR ($CDCl_3$)δ: 2.26 (1H, m), 2.40 (3H, s), 2.75 (1H, m), 3.00 (1H, m), 3.18 (1H, m), 5.70 (1H, t, J=7.0 Hz), 6.87 (1H, s), 7.09 (1H, s), 7.16 (1H, d, J=7.8 Hz), 7.26 (2H, d, J = 8.6 Hz), and 7.40-7.58 (5H, m).

Application Example 9

1-(1H-imidazole-1-yl)-5-(4-methylphenyl)indane·fumarate

^{1}H-NMR (DMSO-d_6)δ: 2.27 (1H, m), 2.34 (3H, s), 2.69 (1H, m), 2.99 (1H, m), 3.20 (1H, m), 5.85 (1H, t, J=7.4 Hz), 6.62 (2H, s), 6.94 (1H, s), 7.08 (1H, d, J=8.0 Hz), 7.10 (1H, s), 7.26 (2H, d, J=8.4 Hz), 7.43-7.64 (4H, m), and 7.78 (1H, s)

[0038] Application Example 10

5-(4-fluorophenyl)-1-(1H-imidazole-1-yl)indane

^{1}H-NMR ($CDCl_3$)δ: 2.26 (1H, m), 2.77 (1H, m), 3.07 (1H, m), 3.18 (1H, m), 5.71 (1H, t, J=7.3 Hz), 6.87 (1H, t, J=1.2 Hz), 7.09 (1H, s), 7.18 (1H, d, J=7.8 Hz), and 7.38-7.60 (7H, m).

Application Example 11

5-(4-chlorophenyl)-1-(1H-imidazole-1-yl)indane·fumarate

^{1}H-NMR (DMSO-d_6)δ: 2.27 (1H, m), 2.70 (1H, m), 3.01 (1H, m), 3.20 (1H, m), 5.88 (1H, t, J=7.0 Hz), 6.63 (2H, s), 6.95 (1H, s), 7.08-7.17 (2H, m), 7.46-7.58 (3H, m), 7.65 (1H, s), 7.69 (2H, d, J=8.6 Hz), and 7.81 (1H, s).

Application Example 12

1-(1H-imidazole-1-yl)-5-(4-methylphenyl)indane

^{1}H-NMR ($CDCl_3$)δ: 2.25 (1H, m), 2.75 (1H, m), 3.04 (1H, m), 3.18 (1H, m), 3.86 (3H, s), 5.71 (1H, t, J=7.0 Hz), 6.88 (1H, s), 6.99 (2H, d, J=8.8 Hz), 7.42 (1H, d, J=8.0 Hz), and 7.48-7.60 (4H, m).

[0039] Application Example 13

1-(1H-imidazole-1-yl)-5-(4-methoxyphenyl)indane·fumarate

^{1}H-NMR (DMSO-d_6)δ: 2.26 (1H, m), 2.69 (1H, m), 3.00 (1H, m), 3.18 /20 (1H, m), 3.80 (1H, m), 5.85 (1H, t, J=7.0 Hz), 6.63 (2H, s), 6.94 (1H, s), 7.02 (2H, d, J=8.6 Hz), 7.08 (1H, d, J=8.0 Hz), 7.11 (1H, s), 7.45 (1H, d, J=8.0 Hz), 7.55-7.65 (3H, m), and 7.79 (1H, s)

Application Example 14

Manufacture of 1-(1H-imidazole-1-yl)-4-phenoxyindane:

Sodium boron hydride (255 mg) was added to a methanol (20 mL)-tetrahydofuran (10 mL) of 4-phenoxy-1-indanone (1.50 g)

being obtained by a method described in Chem. Pharm. Bull., 26, 2475 (1978), and the reaction solution was stirred for 30 min. The reaction solution was enriched, and the residue was dissolved in ethyl acetate, washed with water and a saline solution, and dried. The solvent was distilled off, so that an oily product 4-phenoxy-indanol (1.51 g) was obtained.

^{1}H-NMR ($CDCl_3$)δ: 1.80 (1H, br), 1.96 (1H, m), 2.50 (1H, m), 2.70 (1H, m), 2.97 (1H, m), 5.29 (1H, 5, J=6.2 Hz), 6.80-7.12 (4H, m), and 7.20-7.39 (4H, m)

Dichloromethane (2 mL) solution of thionyl chloride (3.16 g) was dropped into a dichloromethane (25 mL) solution of 4-phenoxy-1-indanol (1.50 g) and refluxed for 1 h after dropping. The reaction solution was enriched, and the residue was dissolved in DMF (25 mL). Imidazole (4.51 g) was added to it and stirred at 100°C for 2 h. The reaction solution was enriched, and the residue was dissolved in ethyl acetate, washed with water and a saline solution, and dried. The solvent was distilled off, and the residue was purified by a silica gel column chromatography (dichloromethane:methanol = 50:1) and recrystallized from dichloromethane-hexane, so that a colorless crystal 1-(1H-imidazole-1-yl)-4-phenoxyindane (1.34 mg) was obtained.

^{1}H-NMR ($CDCl_3$)δ: 2.23 (1H, m), 2.71 (1H, m), 2.87 (1H, m), 3.09 (1H, m), 5.70 (1H, t, J=7.2 Hz), 6.80-7.40 (10H, m), and 7.55 (1H, s).

Next, the compounds of Application Examples 15-24 were synthesized by methods similar to Application Examples 14 and 5.

[0040] Application Example 15

4-(4-fluorophenoxy)-1-(1H-imidazole-1-yl)indane

^{1}H-NMR ($CDCl_3$)δ: 2.24 (1H, m), 2.72 (1H, m), 2.92 (1H, m), 3.10 (1H, m), 5.70 (1H, t, J=7.2 Hz), 6.77-7.10 (8H, m), 7.19 (1H, t, J=7.8 Hz), 6.87-7.70 (4H, m), and 7.55 (1H, s).

Application Example 16

4-(4-fluorophenoxy)-1-(1H-imidazole-1-yl)indane·fumarate

^{1}H-NMR (DMSO-d_6)δ: 2.22 (1H, m), 2.65 (1H, m), 2.77 (1H, m), 3.04 (1H, m), 5.87 (1H, t, J=7.6 Hz), 6.62 (2H, s), 6.81 (2H, dd, J=3.8, 8.0 Hz), 6.93 (1H, s), 7.00-7.14 (3H, m), 7.16-7.30 (3H, m), and 7.77 (1H, s)

Application Example 17

4-(4-chlorophenoxy)-1-(1H-imidazole-1-yl)indane

^{1}H-NMR ($CDCl_3$)δ: 2.23 (1H, m), 2.60-3.15 (3H, m), 5.71 (1H, t, J=7.0 Hz), 6.80-7.32 (9H, m), and 7.55 (1H, s).

Application Example 18

4-(4-chlorophenoxy)-1-(1H-imidazole-1-yl)indane·fumarate

^{1}H-NMR (DMSO-d_6)δ: 2.23 (1H, m), 2.58-3.15 (3H, m), 5.89 (1H, t, J=7.0 Hz), 6.63 (2H, s), 6.85-7.45 (9H, m), and 7.75 (1H, s)

Application Example 19

1-(1H-imidazole-1-yl)-4-(3-methylphenoxy)indane

^{1}H-NMR ($CDCl_3$)δ: 2.23 (1H, m), 2.34 (3H, s), 2.71 (1H, m), 2.89 (1H, m), 3.08 (1H, m), 5.70 (1H, t, J=7.2 Hz), 6.75-6.96 (6H, m), 7.09 (1H, s), 7.15-7.25 (2H, m), and 7.56 (1H, s).

Application Example 20

1-(1H-imidazole-1-yl)-4-(3-methylphenoxy)indane·fumarate

^{1}H-NMR (DMSO-d_6)δ: 2.21 (1H, m), 2.29 (3H, s), 2.65 (1H, m), 2.75 (1H, m), 2.98 (1H, m), 5.88 (1H, t, J=7.4 Hz), 6.62 (2H, s), 6.73-6.88 (4H, m), 6.9-7.00 (2H, m), 7.11 (1H, s), 7.23 (1H, t, J=7.6 Hz), 7.26 (1H, t, J=7.6 Hz), and 7.79 (1H, s)

Application Example 21

4-(3-chlorophenoxy)-1-(4H-1,2,4-triazole-4-yl)indane

^{1}H-NMR ($CDCl_3$)δ: 2.23 (1H, m), 2.70-3.20 (3H, m), 5.80 (1H, t, J=7.0 Hz), 6.85-7.02 (4H, m), 7.12 (1H, m), 7.20-7.33 (2H, m), and 8.15 (2H, s).

Application Example 22

4-(3-chlorophenoxy)-1-(4H-1,2,4-triazole-4-yl)indane·fumarate

^{1}H-NMR (DMSO-d_6)δ: 2.29 (1H, m), 2.70 (1H, m), 2.78 (1H, m), 3.03 (1H, m), 5.99 (1H, t, J=7.2 Hz), 6.63 (2H, s), 6.96 (3H, d,

J=7.8 Hz), 7.08 (1H, t, J=2.0 Hz), 7.20 (1H, br, d, J=8.8 Hz), 7.30 (1H, t, J=8.8 Hz), 7.30 (1H, t, J=7.8 Hz), 7.42 (1H, t, J=8.0 Hz), and 8.60 (2H, s)

Application Example 23

4-(3-chlorophenoxy)-1-(1H-1,2,4-triazole-4-yl)indane

^{1}H-NMR ($CDCl_3$)δ: 2.47 (1H, m), 2.60-3.20 (3H, m), 5.95 (1H, dd, J=6.2, 8.0 Hz), 6.80-7.12 (5H, m), 7.18-7.32 (2H, m), 7.99 (1H, s), and 8.11 (1H, s).

Application Example 24

4-(3-chlorophenoxy)-1-(1H-1,2,4-triazole-4-yl)indane·fumarate

^{1}H-NMR (DMSO-d_6)δ: 2.42 (1H, m), 2.65 (1H, m), 2.82 (1H, m), 2.99 (1H, m), 6.13 (1H, t, J=7.0 Hz), 6.63 (2H, s), 6.95 (3H, d, J=7.8 Hz), 7.05 (1H, m), 7.15-7.32 (2H, m), 7.42 (1H, t, J=8.0 Hz), 8.01 (1H, d, J=3.4 Hz), and 8.71 (1H, d, J=3.4 Hz). /21

Application Example 25

Manufacture of 4-benzoyl-1-(1H-imidazole-1-yl)indane:

Sodium boron hydride (95 mg) was added to a methanol (15 mL)-tetrahydofuran (15 mL) of 4-benzoyl-1-indanone (2.36 g) being obtained by a method described in Chem. Pharm. Bull., 26, 1776 (1978), and the reaction solution was stirred for 30 min. The reaction solution was enriched, and the residue was dissolved in ethyl acetate, washed with water and a saline solution, and dried. The solvent was distilled off, and the

residue was purified by a silica gel column chromatography (hexane:dichloromethane:ethyl acetate = 4:1:1), so that a colorless oily product 4-benzoyl-1-indanol (937 mg) was obtained.

^{1}H-NMR ($CDCl_3$)δ: 1.80-2.20 (2H, m), 2.53 (1H, m), 2.95 (1H, m), 3.19 (1H, m), 5.30 (1H, m), 7.30-7.65 (6H, m), and 7.75-7.82 (2H,m)

Dichloromethane (1 mL) solution of thionyl chloride (1.87 g) was dropped into a dichloromethane (10 mL) solution of 4-benzoyl-1-indanol (937 mg) and refluxed for 1 h after dropping. The reaction solution was enriched, and the residue was dissolved in DMF (20 mL). Imidazole (2.65 g) was added to it and stirred at 100°C for 2 h. The reaction solution was enriched, and the residue was dissolved in ethyl acetate, washed with water and a saline solution, and dried. The solvent was distilled off, and the residue was purified by a silica gel column chromatography (dichloromethane:methanol = 20:1), so that a wax-shaped 4-benzoyl-1-(1H-imidazole-1-yl)indane (763 mg) was obtained.

^{1}H-NMR ($CDCl_3$)δ: 2.26 (1H, m), 2.75 (1H, m), 3.15 (1H, m), 3.32 (1H, m), 5.73 (1H, t, J=7.6 Hz), 6.88 (1H, s), 7.11 (1H, s), 7.25-7.38 (2H, m), 7.45-7.67 (5H, m), and 7.78-7.86 (2H, m).

[0044] Application Example 26

Manufacture of 4-benzoyl-1-(1H-imidazole-1-yl)indane·fumarate:

A methanol solution of fumaric acid (307 mg) was added to 4-benzoyl-1-(1H-imidazole-1-yl)indane (763 mg), and the solvent was enriched. The residue was crystallized from ether, filtered, washed with ether, and dried, so that a colorless crystal 1-(1H-imidazole-1-yl)indane·fumarate (593 mg) was obtained.

^{1}H-NMR (DMSO-d_6)δ: 2.25 (1H, m), 2.66 (1H, m), 3.01 (1H, m), 3.18 (1H, m), 5.92 (1H, t, J=7.4 Hz), 6.63 (2H, s), 6.97 (1H, s), 7.14 (1H, s), 7,.26 (1H, d, J=7.2 Hz), 7.38 (1H, t, J=7.6 Hz), 7.46 (1H, d, J=7.6 Hz), 7.46 (1H, d, J=6.8 Hz), 7.52-7.78 (5H, m), and 7.8 (1H, s)

Next, the compounds of Application Examples 27 and 28 were synthesized by methods similar to Application Example 25 and 26.

Application Example 27

4-(4-clorobenzoyl)-1-(1H-imidazole-1-yl)indane:

^{1}H-NMR ($CDCl_3$)δ: 2.26 (H, m), 2.76 (1H, m), 3.13 (1H, m), 3.32 (1H, m), 5.73 (1H, t, J=7.4 Hz), 6.87 (1H, s), 7.11 (1H, s), 7.27-7.40 (2H, m), 7.41-7.53 (3H, m), 7.59 (1H, s), and 7.77 (2H, d, J=8.6 Hz).

Application Example 28

4-(4-clorobenzoyl)-1-(1H-imidazole-1-yl)indane·fumarate:

^{1}H-NMR (DMSO-d_6)δ: 2.22 (H, m), 2.65 (1H, m), 2.88-3.30 (2H, m), 5.91 (1H, t, J=7.2 Hz), 6.62 (2H, s), 6.95 (1H, s), 7.13

(1H, s), 7,.27 (1H, d, J=7.6 Hz), 7.38 (1H, t, J=7.6 Hz), 7.47 (1H, d, J=7.6 Hz), 7.64 (2H, d, J=8.8 Hz), 7.76 (2H, d, J=8.8 Hz), and 7.80 (1H, s)

[0045] Application Example 29

Manufacture of 1-(1H-imidazole-1-yl)-4-piperidinocarbonylindane:

Diethyl cyanophosphate (2.45 mg) was added to a DMF (15 mL) solution of 4—carboxyl-1-indanone (1.76 g) being obtained by a method described in Chem. Pharm. Bull., 26, 1153 (1978) and piperidine (1.70 g) under ice cooling, and triethylamine (3.03 g) was added to it. The reaction solution was stirred for 30 min, and the reaction solution was enriched. The residue was dissolved in ethyl acetate, washed with water and a saline solution, and dried. The solvent was distilled off, and the residue was purified by a silica gel column chromatography (hexane:ethyl acetate = 1:1), so that a colorless oily product 4-piperidinocarbonyl-1-indanone (2.519 g) was obtained.

^{1}H-NMR ($CDCl_3$)δ: 1.40-1.80 (6H, m), 2.72 (2H, dd, J=5.2, 7.0 Hz), 3.13 (2H, m), 3.28 (2H, m), 3.77 (2H, m), 7.43 (1H, t, J=7.4 Hz), 7.50 (1H, dd, J=1.8, 7.4 Hz), and 7.80 (1H, d, J=1.6, 7.4 Hz)

Sodium boron hydride (380 mg) was added to a methanol (20 mL) of 4-piperidinocarbonyl-1-indanone (2.51 g) under ice cooling, and the reaction solution was stirred for 30 min. The

reaction solution was enriched, and the residue was dissolved in ethyl acetate, washed with water and a saline solution, and dried. The solvent was distilled off, and the residue was recrystallized from dichloromethane-hexane, so that a colorless crystal 4-piperidinocarbonyl-1-indanol (1.553 g) was obtained.

^{1}H-NMR ($CDCl_3$)δ: 1.40-1.70 (6H, m), 1.95 (1H, m), 2.50 (1H, m), 2.81 (1H, m), 3.03 (1H, m), 3.25 (2H, m), 3.73 (2H, m), 5.27 (1H, m), 7.17 (1H, d, J=7.8 Hz), 7.28 (1H, t, J=7.8 Hz), and 7.44 (1H, d, J=7.8 Hz)

Dichloromethane (1 mL) solution of thionyl chloride (1.36 g) was dropped into a dichloromethane (10 mL) solution of 4-piperidinocarbonyl-1-indanol (700 mg) and refluxed for 1 h after dropping. The reaction solution was enriched, and the residue was dissolved in DMF (20 mL). Imidazole (1.94 g) was added to it and stirred at 100°C for 2 h. The reaction solution was enriched, and the residue was dissolved in ethyl acetate, washed with water and a saline solution, and dried. The solvent was distilled off, and the residue was purified by a silica gel column chromatography (dichloromethane:methanol = /22 30:1) and recrystallized from ether, so that a colorless crystal 1-(1H-imidazole-1-yl)-4-piperidinocarbonylindane (249 mg) was obtained.

^{1}H-NMR ($CDCl_3$)δ: 1.40-1.80 (6H, m), 2.24 (1H, m), 2.73 (1H, m), 1.98 (1H, m), 3.14 (1H, m), 3.28 (2H, m), 3.75 (2H, m), 5.68 (1H, t, J=7.4 Hz), 6.84 (1H, s), 7.06-7.15 (2H, m), 7.20-7.30 (2H, m), and 7.55 (1H, s).

[0046] Application Example 30

Manufacture of 4-benzyloxy-1-(1H-imidazole-1-yl)indane:

A mixture of 4-hydroxy-1-indanone (5.0 g), benzyl bromide (6.93 g), calcium carbonate (6.99 g), and dimethylformamide (50 mL) was stirred at room temperature for 24 h. The reaction solution was enriched, and the residue was dissolved in ethyl acetate, washed with water and a saline solution, and dried. The solvent was distilled off, and the residue was washed with hexane, so that a colorless crystal 4-benzyloxy-1-indanone (7.24 mg) was obtained.

^{1}H-NMR ($CDCl_3$)d: 2.69 (2H, t, J=5.8 Hz), 3.11 (2H, t, J=5.8 Hz), 5.17 (2H, s), 7.08 (1H, dd, J=1.4, 7.4 Hz), and 7.25-7.50 (7H, m).

Sodium boron hydride (560 mg) was added to a methanol (10 mL)-tetrahydrofuran (5 mL) solution of 4-benzyloxy-1-indanone (3.5 g), and the reaction solution was stirred for 30 min. The reaction solution was enriched, and the residue was dissolved in ethyl acetate, washed with water and a saline solution, and dried. The solvent was distilled off, and the residue was

crystallized from ethyl acetate/hexane, so that a colorless crystal 4-benzyloxy-1-indanol (3.267 g) was obtained.

^{1}H-NMR ($CDCl_3$)δ: 1.74 (1H, brd, J=5.4 Hz), 1.98 (1H, m), 2.50 (1H, m), 2.81 (1H, m), 3.10 (1H, m), 5.11 (2H, s), 5.26 (1H, m), 6.82 (1H, d, J=7.8 Hz), 7.05 (1H, d, J=7.6 Hz), 7.21 (1H, t, J=7.8 Hz), and 7.30-7.48 (5H, m).

Dichloromethane (2 mL) solution of thionyl chloride (1.99 g) was dropped into a dichloromethane (20 mL) solution of 4-benzyloxy-1-indanol(1.0 g) and refluxed for 1 h after dropping. The reaction solution was enriched, and the residue was dissolved in DMF (20 mL). Imidazole (2.83 g) was added to it and stirred at 100°C for 2 h. The reaction solution was enriched, and the residue was dissolved in ethyl acetate, washed with water and a saline solution, and dried. The solvent was distilled off, and the residue was purified by a silica gel column chromatography (dichloromethane:methanol = 20:1), so that a wax-shaped 4-benzyloxy-1-(1H-imidazole-1-yl)indane (788 mg) was obtained.

^{1}H-NMR ($CDCl_3$)δ: 2.20 (1H, m), 2.71 (1H, m), 2.95 (1H, m), 3.16 (1H, m), 5.14 (2H, s), 5.67 (1H, t, J=7.0 Hz), 6.73 (1H, d, J-7.8 Hz), 6.83 (1H, t, J= 7.8 Hz), 7.30-7.50 (5H, m), and 7.53 (1H, s).

[0047] Application Example 31

Manufacture of 4-benzoyl-1-(1H-imidazole-1-yl)indane·1.5fumarate:

A methanol solution of fumaric acid (310 mg) was added to 4-benzoyl-1-(1H-imidazole-1-yl)indane (788 mg), and the solvent was enriched. The residue was crystallized from ether, filtered, washed with ether, and dried, so that a colorless crystal benzoyl-1-(1H-imidazole-1-yl)indane·1.5fumarate (738 mg) was obtained.

^{1}H-NMR (DMSO-d_6)δ: 2.22 (1H, m), 2.65 (1H, m), 2.65 (1H, m), 2.86 (1H, m), 3.12 (1H, m), 5.17 (2H, s), 5.84 (1H, t, J=7.0 Hz), 6.63 (3H, s), 6.93 (1H, s), 6.98 (1H, t, J=7.0 Hz), 6.63 (3H, s), 6.93 (1H, s), 6.98 (1H, d, J=8.2 Hz), 7.08 (1H, s), 7.18 (1H, t, J=7.8 Hz), 7.32-7.52 (5H, m), and 7.78 (1H, s)

Next, the compounds of Application Examples 32-35 were synthesized by methods similar to Application Example 30 and 31.

Application Example 32

4-(2-chlorobenzyloxy)-1-(1H-imidazole-1-yl)indane

^{1}H-NMR ($CDCl_3$)δ: 2.21 (1H, m), 2.74 (1H, m), 3.00 (1H, m), 3.20 (1H, m), 5.23 (2H, s), 5.69 (1H, t, J=7.0 Hz), 6.76 (1H, d, J=7.4 Hz), 6.84 (1H, s), 6.88 (1H, d, J=8.0 Hz), 7.07 (1H, s), 7.21 (1H, t, J=8.0 Hz), 7.26-7.47 (3H, m), and 7.50-7.61 (2H, m).

Application Example 33

4-(3-chlorobenzyloxy)-1-(1H-imidazole-1-yl)indane

^{1}H-NMR ($CDCl_3$)δ: 2.23 (1H, m), 2.73 (1H, m), 2.96 (1H, m), 3.18 (1H, m), 5.11 (2H, s), 5.69 (1H, t, J=7.2 Hz), 6.75 (1H, d, J=7.8 Hz), 6.83 (1H, d, J=7.8 Hz), 6.84 (1H, t, J=1.2 Hz), 7.07 (1H, s), 7.20 (1H, t, J=7.8 Hz), 7.50-7.56 (3H, m), 7.45 (1H, s), and 7.54 (1H, s).

Application Example 34

4-(3-chlorobenzyloxy)-1-(1H-imidazole-1-yl)indane·fumarate

^{1}H-NMR ($CDCl_3$)δ: 2.23 (1H, m), 2.66 (1H, m), 2.88 (1H, m), 3.12 (1H, m), 5.19 (2H, s), 5.85 (1H, t, J=7.0 Hz), 6.63 (2H, s), 6.64 (1H, d, J=7.8 Hz), 6.94 (1H, s), 6.96 (1H, s), 6.96 (1H, d, J=8.0 Hz), 7.08 (1H, s), 7.19 (1H, t, J=8.0 Hz), 7.37-7.48 (3H, m), 7.54 (1H, s), and 7.79 (1H, s).

Application Example 35

4-(4-chlorobenzyloxy)-1-(1H-imidazole-1-yl)indane

^{1}H-NMR ($CDCl_3$)δ: 2.20 (1H, m), 2.72 (1H, m), 2.94 (1H, m), 3.17 (1H, m), 5.10 (2H, s), 5.68 (1H, t, J=7.0 Hz), 6.74 (1H, d, J=7.6 Hz), 6.83 (1H, t,/23 J=1.2 Hz), 6.84 (1H, d, J=8.0 Hz), 7.07 (1H, s), 7.20 (1H, t, J=8.0 Hz), 7.39 (4H, s), and 7.54 (1H, s).

[0049] Application Example 36

5-benzyloxy-1-(1H-imidazole-1-yl)tetralin

Dichloromethane (1 mL) solution of thionyl chloride (2.81 g; 23.6 mmol) was dropped into a dichloromethane (25 mL) solution of 5-benzyloxy-1,2,3,4-tetrahydro-1-naphthol (1.5 g; 5.9 mmol) and refluxed for 1 h after dropping. The reaction solution was enriched, and the residue was dissolved in DMF (20 mL). Imidazole (4.016 g; 59 mmol) was added to it and stirred at 100°C for 2 h. The reaction solution was enriched, and the residue was dissolved in ethyl acetate, washed with water and a saline solution, and dried. The solvent was distilled off, and the residue was purified by a silica gel column chromatography (dichloromethane:methanol = 30:1) and recrystallized from dichloromethane-hexane, so that a milky white crystal 5-benzyloxy-1-(1H-imidazole-1-yl)tetralin (1.093 g; 61%) was obtained.

mp.: 109-110°C (CH_2Cl_2-hexane)

IR (KBr): 1582, 1492, 1470, 1314, 1285, and 1254 cm^{-1}

^{1}H-NMR ($CDCl_3$)d: 1.75-1.93 (2H, m), 2.00-2.30 (2H, m), 2.85 (2H, m), 5.10 (2H, s), 5.33 (1H,, t, J=6.6 Hz), 6.52 (1H, d, J=7.8 Hz), 6.83 (1H, s), 6.85 (1H, d, J= 7.4 Hz), 7.06 (1H, s), 7.10 (1H, t, J=7.8 Hz), and 7.28-7.50 (6H, m).

Element analysis value: $C_20H_20N_2O$

Calculated value: 78.92 C, 6.62 H, and 9.20 N

Experimental value: 78.84 C, 6.55 H, and 9.16 N

Application Example 37

5-(2-chlorobenzyloxy)-1-(1H-imidazole-1-yl)tetralin

Similarly to Application Example 36, using 5-(2-chlorobenzyloxy)-1,2,3,4-tetrahydro-1-naphthol obtained in Referential Example 5 instead of the 5-benzyloxy-1,2,3,4-tetrahydro-1-naphthol, 5-(2-chlorobenzyloxy)-1-(1H-imidazole-1-yl)tetralin was obtained.

Yield: 65%

mp.: 103-104°C (Et_2O)

IR (KBr): 1585, 1462, 1253, 1224, 1074, and 1049 cm^{-1}

^{1}H-NMR ($CDCl_3$)d: 1.80-2.30 (4H, m), 2.89 (2H, m), 5.19 (2H, s), 5.34 (1H,, t, J=6.2 Hz), 6.54 (1H, d, J=7.6 Hz), 6.84 (1H, s), 6.86 (1H, d, J= 8.2 Hz), 7.06 (1H, s), 7.11 (1H, t, J=8.0 Hz), 7.25-7.48 (4H, m), and 7.60 (1H, m)

Element analysis value: $C_{20}H_{19}ClN_2O$

Calculated value: 70.90 C, 5.65 H, and 8.27 N

Experimental value: 70.84 C, 5.69 H, and 8.25 N

[0050] Application Example 38

5-(3-chlorobenzyloxy)-1-(1H-imidazole-1-yl)tetralin

Similarly to Application Example 36, using 5-(3-chlorobenzyloxy)-1,2,3,4-tetrahydro-1-naphthol obtained in Referential Example 6 instead of the 5-benzyloxy-1,2,3,4-

tetrahydro-1-naphthol, 5-(3-chlorobenzyloxy)-1-(1H-imidazole-1-yl)tetralin was obtained.

Yield: 53%

mp.: 72-73°C (Et_2O-hexane)

IR (KBr): 1582, 1470, 1451, 1316, 1266, and 1252 cm^{-1}

^1H-NMR ($CDCl_3$)d: 1.80-2.30 (4H, m), 2.80-3.00 (2H, m), 5.07 (2H, s), 5.34 (1H,, t, J=6.2 Hz), 6.53 (1H, d, J=7.6 Hz), 6.81 (1H, d, J= 8.0 Hz), 6.83 (1H, s), 7.06 (1H, s), 7.10 (1H, t, J=8.0 Hz), 7.30-7.40 (3H, m), and 7.46 (2H, s)

Element analysis value: $C_{20}H_{19}ClN_2O \cdot 2H_2O$

Calculated value: 70.15 C, 5.71 H, and 8.18 N

Experimental value: 70.32 C, 5.63 H, and 8.08 N

Application Example 39

5-phenoxy-1-(1H-imidazole-1-yl)tetralin

Dichloromethane (1 mL) solution of thionyl chloride (2.0 g; 16.8 mmol) was dropped into a dichloromethane (15 mL) solution of 5-phenoxy-1,2,3,4-tetrahydro-1-naphthol obtained in Referential Example 8 and refluxed for 1 h after dropping. The reaction solution was enriched, and the residue was dissolved in DMF (20 mL). Imidazole (2.04 g; 30 mmol) was added to it and stirred at 100°C for 2 h. The reaction solution was enriched, and the residue was dissolved in ethyl acetate, washed with water and a saline solution, and dried. The solvent was

distilled off, and the residue was purified by a silica gel column chromatography (dichloromethane:methanol = 30:1) and recrystallized from ether-hexane, so that a milky white crystal 5-phenoxy-1-(1H-imidazole-1-yl)tetralin (551 mg; 61%) was obtained.

mp.: 138-139°C (Et20-hexane)

IR (KBr): 1577, 1489, 1456, 1242, and 1211 cm^{-1}

^{1}H-NMR ($CDCl_3$)d: 1.75-1.95 (2H, m), 2.00-2.30 (2H, m), 2.82 (2H, m), 5.37 (1H,, t, J=6.2 Hz), 6.68 (1H, d, J=7.6 Hz), 6.83 (1H, d, J= 8.8 Hz), 6.86 (1H, s), 6.95 (2H, d, J=7.4 Hz), 7.04-7.15 (3H, m), 7.34 (2H, t, J=7.4 Hz), and 7.49 (1H, s).

Element analysis value: $C_{19}H_{18}N_2O$

Calculated value: 78.59 C, 6.25 H, and 9.65 N

Experimental value: 78.36 C, 6.42 H, and 9.49 N

[0051] Application Example 40

7-benzyloxy-3-(3-pyridyl)indene

Under a nitrogen atmosphere, 2 M aqueous sodium carbonate solution (3.8 mL, 7.6 mmol) was added to a dimethoxyethane (20 mL) solution of 7-benzyloxy-3-trifluoromethanesulfonyloxyindene (1.42 g; 3.8 mmol), diethyl-3-pyridylborane (6737 mg;; 4.5 mmol), and tetrakistriphenylphosphine palladium (0) /24 (500 mg; 0.4 mmol) and stirred at 100°C for 15 h. The reaction solution was diluted with ethyl acetate, washed with water and a

saline solution, and dried. The solvent was distilled off, and the residue was purified by a silica gel column chromatography (hexane:ethyl acetate:dichloromethane = 6:2:1) and recrystallized from ethyl acetate-hexane, so that a brown crystal 7-benzyloxy-3-(3-pyridyl)indene (480 mg; 42%) was obtained.

mp.: 108-110°C (AcOEt-hexane)

IR (KBr): 1607, 1586, 1575, 1480, 1463, 1310, 1262, 1245, and 1059 cm^{-1}

^{1}H-NMR ($CDCl_3$)d: 3.57 (2H, d , J=2.2 Hz), 5.22 (2H, s), 6.68 (1H, t, J=2.2 Hz), 6.89 (1H, d, J=8.0 Hz), 7.18 (1H, d, J= 7.6 Hz), 7.30-7.55 (7H, m), 7.90 (1H, dt, J=2.2, 7.6 Hz), 8.61 (1H, dd, J=1.6, 4.8 Hz), and 8.86 (1H, d, J=2.2 Hz).

Element analysis value: $C_{31}H_{17}NO \cdot 0.5H_2O$

Calculated value: 81.79 C, 5.88 H, and 4.54 N

Experimental value: 81.85 C, 5.68 H, and 4.16 N

[0052] Comparative Example 1

5-benzyloxy-1-tetralon

A mixture of 5-hydroxy-1-tetralon (47,950 mg; 5.86 mmol), benzyl bromide (1.20 g; 7.02 mmoml), potassium carbonate (1.21 g; 8.77 mmol), and dimethylformamide (18 mL) was stirred at room temperature for 24 h. The reaction was enriched, and the residue was dissolved in ethyl acetate, washed with water and a

saline solution, and dried. The solvent was distilled off, and the residue was washed with hexane, so that a colorless oily product 5-benzyloxy-1-tetralon (1.50 g; 100%) was obtained.

IR (Neat): 1683, 1279, and 1262 cm^{-1}

^{1}H-NMR ($CDCl_3$)d: 2.13 (2H, m), 2.65 (2H, t, J=6.0 Hz), 2.98 (2H, t, J=6.0 Hz), 5.12 (2H, s), 7.09 (1H, dd, J= 1.2, 8.0 Hz), 7.26 (1H, t, J=8.0 Hz), 7.30-7.50 (5H, m), and 7.68 (1H, dd, J=1.2, 8.0 Hz).

Comparative Example 2

5-(2-chlorobenzyloxy)-1-tetralon

Using a method similar to that of Referential Example 1, 5-(2-chlorobenzyloxy-1-tetralon was obtained using 2-chlorobenzyl bromide instead of the benzyl bromide.

Yield: 89%

IR (KBr): 1681, 1580, 1478, 1441, 1281, 1262, and 1249 cm^{-1}

^{1}H-NMR ($CDCl_3$)d: 2.14 (2H, m), 2.64 (2H, dd, J=5.8, 7.2 Hz), 3.00 (2H, t, J=6.0 Hz), 5.19 (2H, s), 7.09 (1H, dd, J= 1.2, 8.0 Hz), 7.20-7.45 (4H, m), 7.55 (1H, m), and 7.69 (1H, dd, J=1.2, 7.8 Hz).

[0053] Comparative Example 3

5-(3-chlorobenzyloxy)-1-tetralon

Using a method similar to that of Referential Example 1, 5-(3-chlorobenzyloxy-1-tetralon was obtained using 3-chlorobenzyl bromide.

Yield: 94%

IR (KBr): 1679, 1598, 1582, 1478, 1441, 1382, 1285, and 1272 cm^{-1}

^{1}H-NMR ($CDCl_3$)d: 2.13 (2H, m), 2.64 (2H, dd, J=5.6, 7.2 Hz), 2.97 (2H, t, J=6.0 Hz), 5.07 (2H, s), 7.04 (1H, dd, J= 1.0, 8.0 Hz), 7.20-7.35 (4H, m), 7.44 (1H, s), and 7.68 (1H, dd, J=1.0, 8.0 Hz).

Referential Example 4

5-benzyloxy-1,2,3,4-tetrahydro-1-naphthol

A sodium boron hydride (226 mg; 5.95 mmol) was added to a methanol (20 mL) suspension solution of 5-benzyloxy-1-tetralon (1.5 g; 5.95 mmol), and the reaction solution was stirred for 30 min. The reaction solution was enriched, and the residue was dissolved in ethyl acetate, washed with water and a saline solution, and dried. The solvent was distilled off, and the residue was crystallized from hexane, so that a colorless crystal 5-benzyloxy-1,2,3,4-tetralon-1-naphthol (1.513 g; 100%) was obtained.

IR (KBr): 3367, 1580, 1455, 1262, and 1247 cm-1

^{1}H-NMR ($CDCl_3$)d: 1.68-2.04 (4H, m), 2.62 (1H, m), 2.87 (1H,, dt, J=4.6, 17.8 Hz), 4.78 (1H, m), 5.07 (2H, s), 6.82 (1H, d, J=7.8 Hz), 7.08 (1H, d, J= 7.8 Hz), 7.18 (1H, t, J=7.8 Hz), and 7.26-7.48 (5H, m).

Element analysis value: $C_20H_20N_2O$

Calculated value: 78.92 C, 6.62 H, and 9.20 N

Experimental value: 78.84 C, 6.55 H, and 9.16 N

[0054] Comparative Example 5

5-(2-chlorobenzyloxy)-1,2,3,4-tetrahydro-1-naphthol

A reaction similar to that of Referential Example 4 was carried out using 5-(2-chlorobenzyloxy)-1-tetrolon, so that 5-(2-chlorobenzyloxy)-1,2,3,4-tetrahydro-1-naphthol was obtained.

Yield: 95%

IR (KBr): 1583, 1475, 1448, 1257, and 1047 cm^{-1}

^{1}H-NMR ($CDCl_3$)d: 1.75-2.05 (4H, m), 2.68 (1H, m), 2.90 (1H, m), 4.79 (1H, m), 5.16 (2H, s), 6.83 (1H, d, J=7.8 Hz), 7.07-7.43 (6H, m), and 7.58 (1H, m).

Comparative Example 6

5-(3-chlorobenzyloxy)-1,2,3,4-tetrahydro-1-naphthol

A reaction similar to that of Referential Example 4 was carried out using 5-(3-chlorobenzyloxy)-1-indanone, so that 5-(3-chlorobenzyloxy)-1,2,3,4-tetrahydro-1-naphthol was obtained.

Yield: 100%

IR (Neat): 1583, 1456, and 1249 cm^{-1}

^{1}H-NMR ($CDCl_3$)d: 1.75-2.05 (4H, m), 2.63 (1H, m), 2.87 (1H, m), 4.79 (1H, m), 5.04 (2H, s), 6.77 (1H, d, J=7.8 Hz), 7.07-7.35 (6H, m), and 7.43 (1H, s).

[0055] Referential Example 7

5-phenoxy-1-tetralon

A mixture of 5-phenoxy-1-tetralon (5 g: 31 mmol), iodobenzene (12.59 g; 62 mmol), calcium carbonate (2.259 g; 31 mmol), and pyridine (50 mL0 was heated and refluxed, and copper oxide (3.7 g; 46 mmol) was added to it and refluxed for 12 h. Toluene (50 mL) and methanol (50 mL) were added to the/25 reaction solution and filtered, and the filtrate was diluted with ethyl acetate, washed with 1 N hydrochloric acid, water, and saline solution, and dried. The solvent was distilled off, and the residue was purified by a silica gel column chromatography (hexane:ethyl acetate = 5:1), so that a colorless crystal 5-phenoxy-1-tetralon (740 mg; 10%) was obtained.

IR (KBr): 1685, 1489, 1277, and 1240 cm^{-1}

^{1}H-NMR ($CDCl_3$)d: 2.11 (2H, quint, J=6.0 Hz), 2.66 (2H, t, J=6.0 Hz), 2.92 (2H, t, J=6.0 Hz), 6.86-7.00 (2H, m), 7.03-7.13 (2H, m), 7.21-7.40 (3H, m), and 7.87 (1H, dd, J=1.2, 7.8 Hz).

Referential Example 8

5-phenoxy-1,2,3,4-tetrahydro-1-naphthol

A sodium boron hydride (150 mg; 3.95 mmol) was added to a methanol (10 mL) suspension solution of 5-phenoxy-1-tetralon (740 mg; 3.11 mmol), and the reaction solution was stirred for 30 min. The reaction solution was enriched, and the residue was dissolved in ethyl acetate, washed with water and a saline solution, and dried. The solvent was distilled off, so that a colorless oily product 5-phenoxy-1,2,3,4-tetralon-1-naphthol was obtained.

IR (Neat): 3271, 1577, 1489, 1456, 1240, and 1213 cm^{-1}

^{1}H-NMR ($CDCl_3$)d: 1.62-2.03 (4H, m), 2.50-2.88 (2H, m), 4.82 (1H, m), 6.78-6.95 (3H, m), 7.04 (1H, t, J=7.4 Hz), and 7.11-7.40 (4H, m).

Referential Example 9

7-benzyloxy-3-trifluoromethanesulfonyloxyindene

A dichloromethane (2 mL) solution of trifluoromethanesulfonic anhydride (1.30 g; 4.6 mmol) was dropped into a dichloromethane (20 mL) solution of 4-benzyloxy-1-indenone (1.0 g; 4.2 mmol) and 2.6-di-tert-butylpyridine (1.04 g; 5.44 mmol) and refluxed for 15 min after dropping. The reaction solution was diluted with ethyl acetate, washed with water, aqueous citric acid solution, and saline solution, and dried. The solvent was distilled off, and the residue was purified by a silica gel column chromatography (hexane:ethyl

acetate = 10:1), so that a colorless oily product 7-benzyloxy-3-trifluoromethanesulfonyloxyindene (1.42 g; 91%) was obtained.

IR (Neat): 1575, 1425, 1250, 1210, and 1135 cm^{-1}

^1H-NMR ($CDCl_3$)d: 3.47 (2H, j, J=2.2 Hz), 5.17 (2H, s), 6.38 (1H, t, J-2.2 Hz), 6.91 (1H, d, J=8.2 Hz), 7.07 (1H, d, J=7.4 Hz), and 7.25-7.50 (6H, m).

Test Example 1

Measurement of rat steroid C_{17-20} lyase inhibition activity

It was measured according to The Prostate, Vol. 26, 140-150 (1995). A testicle was extracted from a male SD rat at an age of 10 weeks, and the testicle was homogenized and centrifuged, so that a microsome was prepared. [1,2-^3H]-17α-hydroxyprogesterone with a final concentration of 10 nM, NADPH solution, and test compound were dissolved in 100 mM phosphoric acid buffer solution with pH of 7.4, and 10 μg/10 μL microsome protein was added to it and incubated at 37°C for 7 min. 40 μL ethyl acetate was added to it and centrifuged, and the matrix and the product (andorostendione and testosterone) in the supernatant fluid were separated by a silica gel thin-layer chromatography (TLC). The spot was detected and quantified by BAS2000 Bioimage Analyzer. When the test compound was not added (control group), the amount of product was assumed as 100%, and the compound concentration (IC_{50} value) required for suppressing

the amount of product to 50%, compared with the control group, was calculated. They are shown in Table 2.

(Table 2)

化合物 (実施例番号)	IC_{50} (nM)
5	29
7	36
9	45
14	29
16	22
20	35
32	59
Ketoconazole	160

1. Compound (application example No.)

[0057]

(Effects of the invention)

The compound or its salt of the present invention has a steroid C_{17-20} lyase inhibition activity and is useful for treating and preventing medicine for various kinds of diseases, for example, cancers of malignant tumors, their transfer and regeneration, symptoms due to these cancers, prostatic hypertrophy masculinization, hypertrichosis, breast cancer, uterine cancer, mastitis, hysteromyoma, endometriosis, etc., for mammal animals.